CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 10/24/97

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SLIDES (Clopidogrel Presentation)

Clopidogrel Review

Cardiovascular and Renal Drugs
Advisory Committee Meeting
October 24, 1997

GEORGE CLAY, Ph.D.

VICE PRESIDENT, REGULATORY AFFAIRS
SANOFI PHARMACEUTICALS, INC.

Presentation Agenda

Overview of CAPRIE	J. Donald Easton, M.D.
Statistical Interpretation of CAPRIE	Lloyd Fisher, Ph.D.
Clinical Interpretation of CAPRIE	Alison Pilgrim, M.D., Ph.D.
Conclusions	George A. Clay, Ph.D.

Consultants

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PROVIDENCE, RHODE ISLAND

CAPRIE STEERING COMMITTEE
CAPRIE CENTRAL VALIDATION COMMITTEE

Atherosclerosis

- Major pathological process underlying stroke and myocardial infarction
- Usually generalized - affecting more than one vascular bed
- Annual incidence in the U.S.:
  - 1.5 M myocardial infarctions
  - 0.5 M strokes
- Platelets play a pivotal role in acute thrombotic events
- Antiplatelet agents are the primary treatment for preventing these events

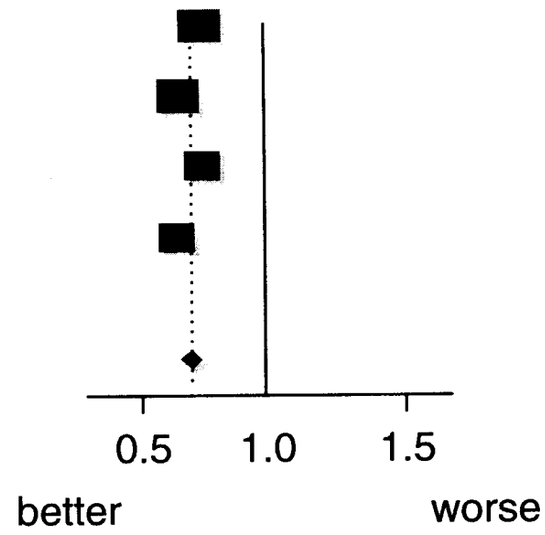
Antiplatelet Trialists' Collaboration Meta-Analysis

- Meta-analysis of all published and unpublished unconfounded randomized trials available March 1990
- Trials identified by literature search, trial registry and inquiry of investigators and pharmaceutical manufacturers
- Clear definitions of endpoints
- Well defined statistical methodology

BMJ 1994; 308; 81-106

Antiplatelet Trialists' Collaboration Meta-Analysis

	MI/Stroke/Vascular Death		Odds ratio & CI	% Odds reduction
	Antiplatelet	Control		
Prior MI	13.5%	17.1%		25%
Acute MI	10.6%	14.4%		29%
Prior Stroke / TIA	18.4%	22.2%		22%
Other High Risk	6.9%	9.2%		32%
ALL HIGH RISK	11.4%	14.7%		27%



BMJ 1994; 308; 81-106

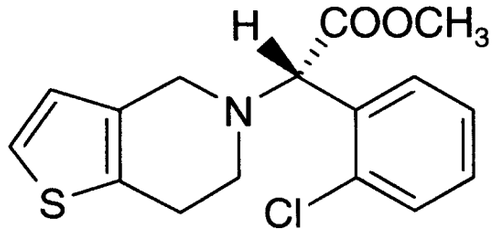
Antiplatelet Trialists' Collaboration Meta-Analysis

MI/Stroke/Vascular Death

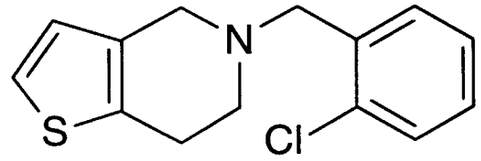
- Odds reduction of antiplatelet agents:
  - aspirin vs. placebo 25%
  - ticlopidine vs. placebo 33%
  - ticlopidine vs. aspirin 10%

BMJ 1994; 308; 81-106

Clopidogrel



Clopidogrel



Ticlopidine

- A thienopyridine related to ticlopidine
- Common mode of action - blockade of platelet ADP receptor
- Dose chosen to be equipotent with approved dose of ticlopidine based on:
  - platelet aggregation
  - bleeding time

CAPRIE

Clopidogrel versus **A**spirin in **P**atients at **R**isk of **I**schemic **E**vents

Rationale for CAPRIE

- Patients with a wide spectrum of atherosclerotic disease are at risk of all major atherothrombotic events.
- Atherothrombotic process is similar regardless of clinical manifestation of underlying atherosclerosis.
- Clopidogrel is expected to benefit the entire spectrum of atherosclerotic patients.

Study Overview

- Compare the efficacy and safety of clopidogrel to the active control aspirin
- Blinded, randomized in 2 parallel groups:
  - clopidogrel = 75 mg once daily
  - aspirin = 325 mg once daily
- Multicenter, multinational trial (304 centers in 16 countries)
- 1-3 years of treatment
- 19,185 patients enrolled and followed-up regardless of discontinuation of study drug

Patient Population

- Qualifying Conditions (one of the following):
  - Ischemic Stroke (IS): 1 week to 6 months
  - Myocardial Infarction (MI): within 35 days
  - Peripheral Arterial Disease (PAD): current intermittent claudication or prior arterial intervention
- Patients with prior atherothrombotic events or atherosclerotic disease in more than one vascular bed were not excluded.
- Patients with known intolerance to aspirin were excluded

Outcome Events

- Non-fatal events
  - myocardial infarction
  - ischemic stroke
  - intracranial hemorrhage
  - leg amputation
- Fatal events
  - myocardial infarction*
  - ischemic stroke*
  - hemorrhage
  - non-vascular
  - other vascular*

* Components of "vascular death"

Protocol Outcome Clusters

- Primary
  - Ischemic stroke, MI, or vascular death
- Secondary
  - Ischemic stroke, MI, amputation, or vascular death
  - Vascular death
  - Any stroke, MI, or death from any cause
  - Death from any cause

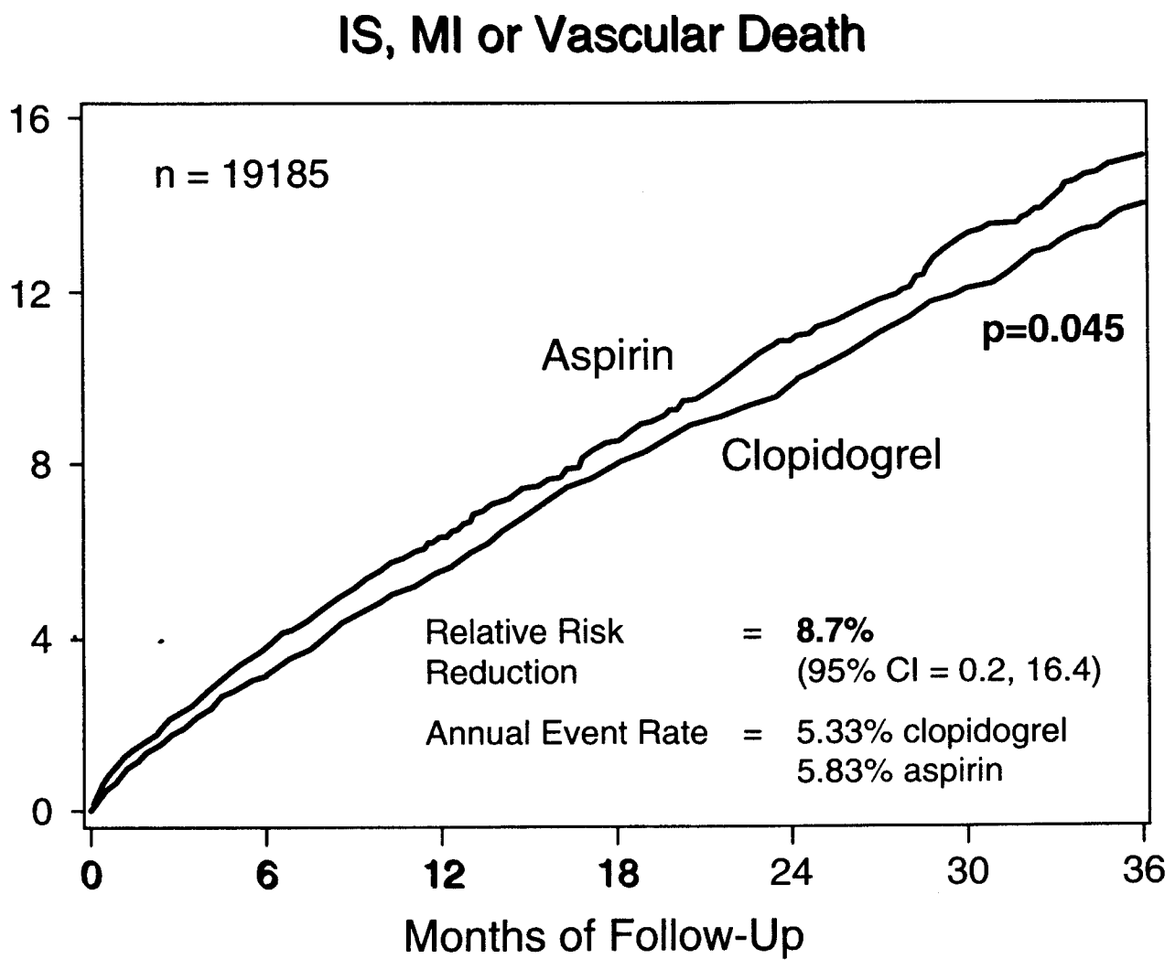
Patient Randomization

Qualifying Condition	clopidogrel	aspirin	Total
IS	3233	3198	6431
MI	3143	3159	6302
PAD	3223	3229	6452
Total	9599	9586	19185

Patient Accountability

	No. (%) of Patients with Events	
	clopidogrel n=9599	aspirin n=9586
Patients not receiving study drug	46 (0.5)	40 (0.4)
Patients lost to follow-up	30 (0.3)	26 (0.3)
Early permanent discontinuations of study drug	2286 (23.8)	2311 (24.1)
Patients taking more than 80% of prescribed study drug	8193 (86.0)	8098 (85.1)

Primary Analysis



Primary Outcome Cluster

	No. (%) of Patients with Events	
	clopidogrel n=9599	aspirin n=9586
IS, MI or Vascular Death	939 (9.8)	1020 (10.6)
IS (fatal or not)	438 (4.6)	461 (4.8)
MI (fatal or not)	275 (2.9)	333 (3.5)
Other vascular death	226 (2.4)	226 (2.4)

Primary Outcome by Geographic Region

Region	No. of Patients with Events		RRR % (95% CI)
	clopidogrel	aspirin	
Europe and Australasia n = 11460	538	577	7.0 (-4.6, 17.3)
North America n = 7725	401	443	10.9 (-1.9, 22.2)

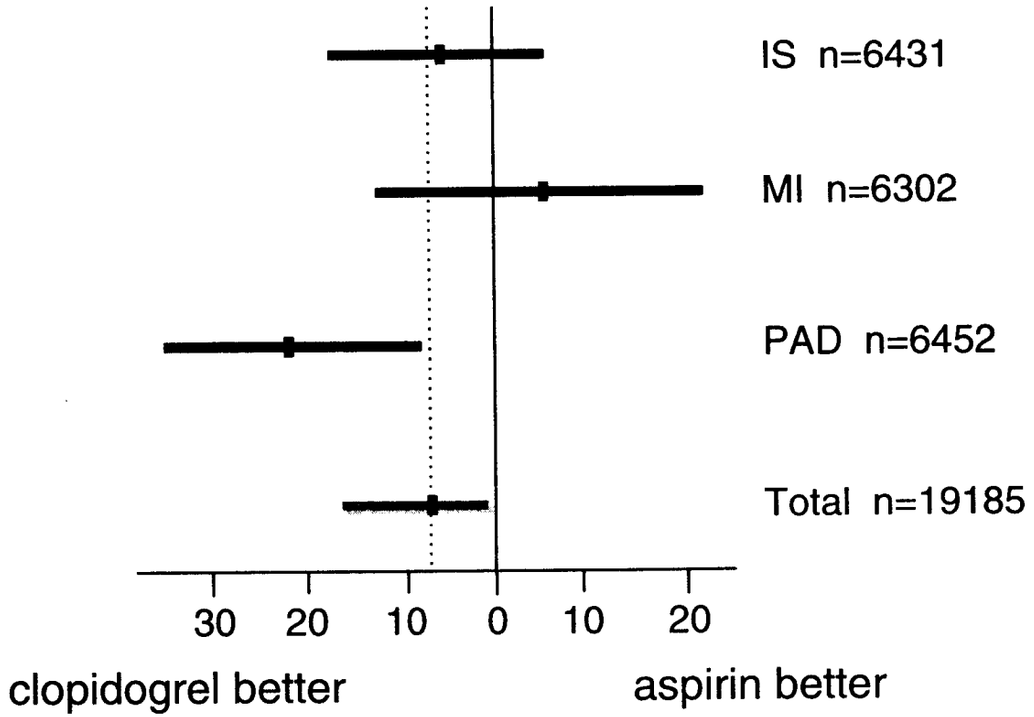
RRR = Relative Risk Reduction

Primary Outcome by Qualifying Condition

Qualifying Condition	RRR %	95% CI
IS	7.3	(-5.7, 18.7)
MI	-4.0	(-22.5, 11.7)
PAD	23.7	(8.9, 36.2)

RRR = Relative Risk Reduction

Relative Risk Reduction by Qualifying Condition



Secondary Analyses

Outcome Event	No. of Patients with Events		RRR % (95% CI)
	clopidogrel n=9599	aspirin n=9586	
IS, MI, amputation, or vascular death	979	1050	7.5 (-0.9, 15.2)
Any stroke, MI, or death from any cause	1133	1206	6.9 (-0.9, 14.2)
Vascular death	350	378	7.6 (-6.9, 20.1)
Death from any cause	560	571	2.2 (-9.9, 12.9)

RRR = Relative Risk Reduction

CAPRIE - Adverse Events

Event	Adverse Events (% of Patients)	
	clopidogrel n=9599	aspirin n=9586
Any Rash	6.02***	4.61
Gastrointestinal	27.14	29.82***
Diarrhea	4.46***	3.36
Ulcers	0.68	1.15***
GI Bleeding	1.99	2.66**
Intracranial Hemorrhage	0.35	0.49
Neutropenia (<1.2 G/L)	0.10	0.16
Thrombocytopenia (<100 G/L)	0.23	0.23

** $p \leq 0.01$ *** $p \leq 0.001$

CAPRIE - Clopidogrel Safety

- >15,000 patient-years experience
- Good overall tolerability
- Low discontinuation rate due to adverse events - similar to aspirin
- Low incidence of rash or diarrhea
- No excess of thrombocytopenia or neutropenia
- Significantly less GI bleeding and better overall GI tolerability than aspirin

CAPRIE - Key Points

- Large well conducted study
- Clopidogrel was compared with an effective active control - aspirin
- Clopidogrel was more effective than aspirin in the predefined primary analysis.
- Clopidogrel safety profile at least as good as aspirin

LLOYD FISHER, Ph.D.

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Statistical Issues

- How would clopidogrel compare with placebo if such a trial were ethical?
- How robust is the observed differential treatment effect by qualifying condition subgroup (called an interaction)?

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Antiplatelet Trialists' Collaboration Meta-Analysis

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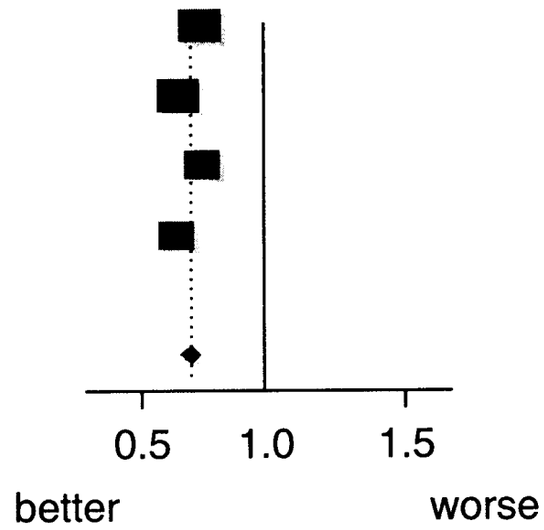


BMJ 1994; 308; 81-106

How Might Clopidogrel Have Done Against a Placebo?

- Because there was no evidence of heterogeneity (p=0.994), all aspirin versus placebo secondary prevention trials were used for the comparison with the overall CAPRIE population.
- Analyses of the CAPRIE qualifying condition subgroups used trials in comparable clinical conditions.
  - acute or prior MI
  - prior stroke/TIA

How Might Clopidogrel Have Done Against a Placebo?

- Four endpoints were examined:
  - All strokes, MIs or vascular deaths
  - All strokes, MIs or death from any cause
  - Vascular deaths
  - All deaths
- Equivalent events were used from both the meta-analysis and CAPRIE.

How Might Clopidogrel Have Done Against a Placebo?

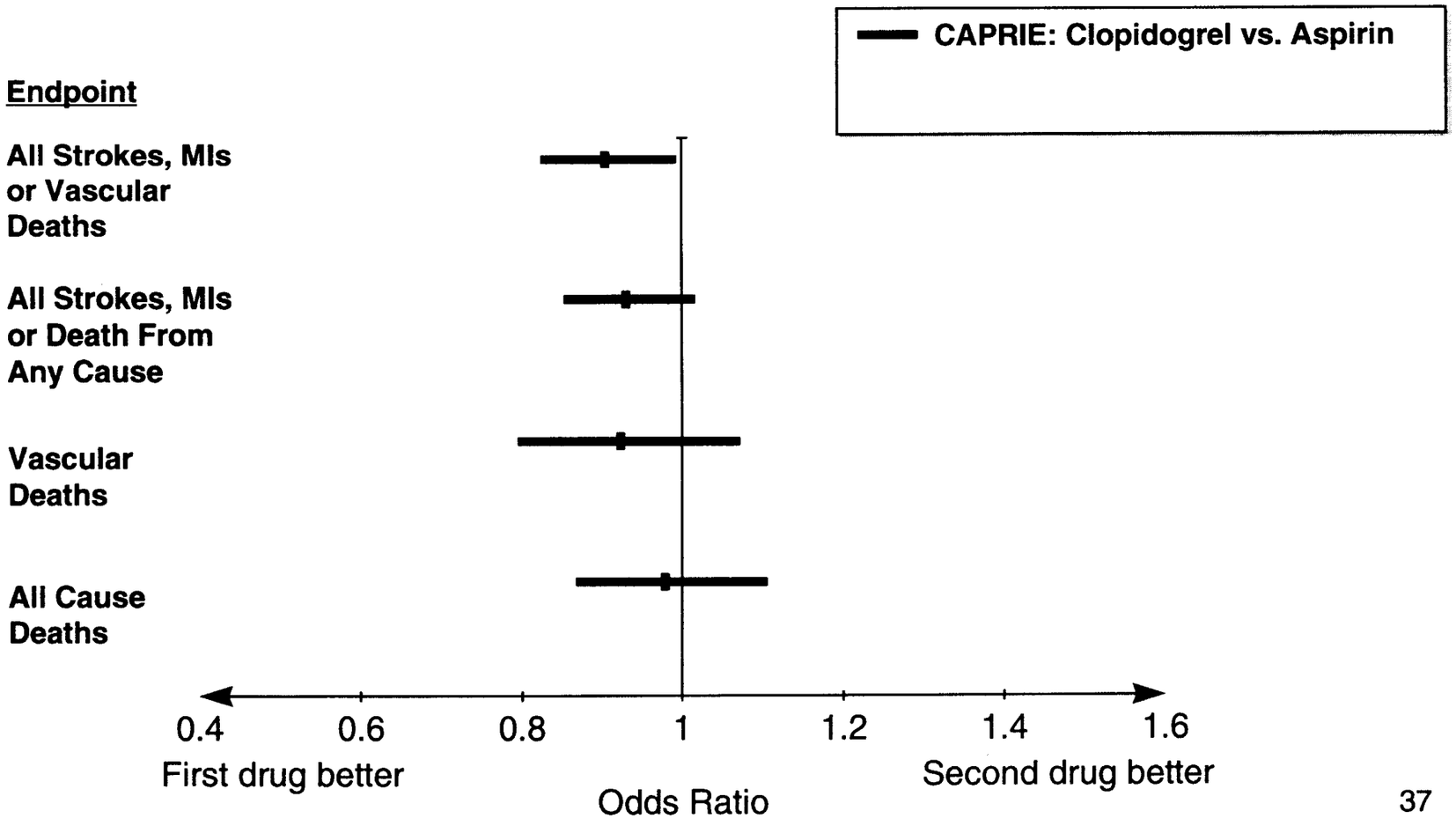
- Odds ratios are used with the assumption that the aspirin/placebo odds ratio would have been observed if there had been a placebo arm in the CAPRIE trial.

How Might Clopidogrel Have Done Against a Placebo?

- The analyses are presented graphically:
  - for the whole study
  - for the MI subgroup
  - for the stroke subgroup

Clopidogrel vs. Synthetic Placebo Control
Odd Ratios and 95% Confidence Intervals

Overall Patient Population



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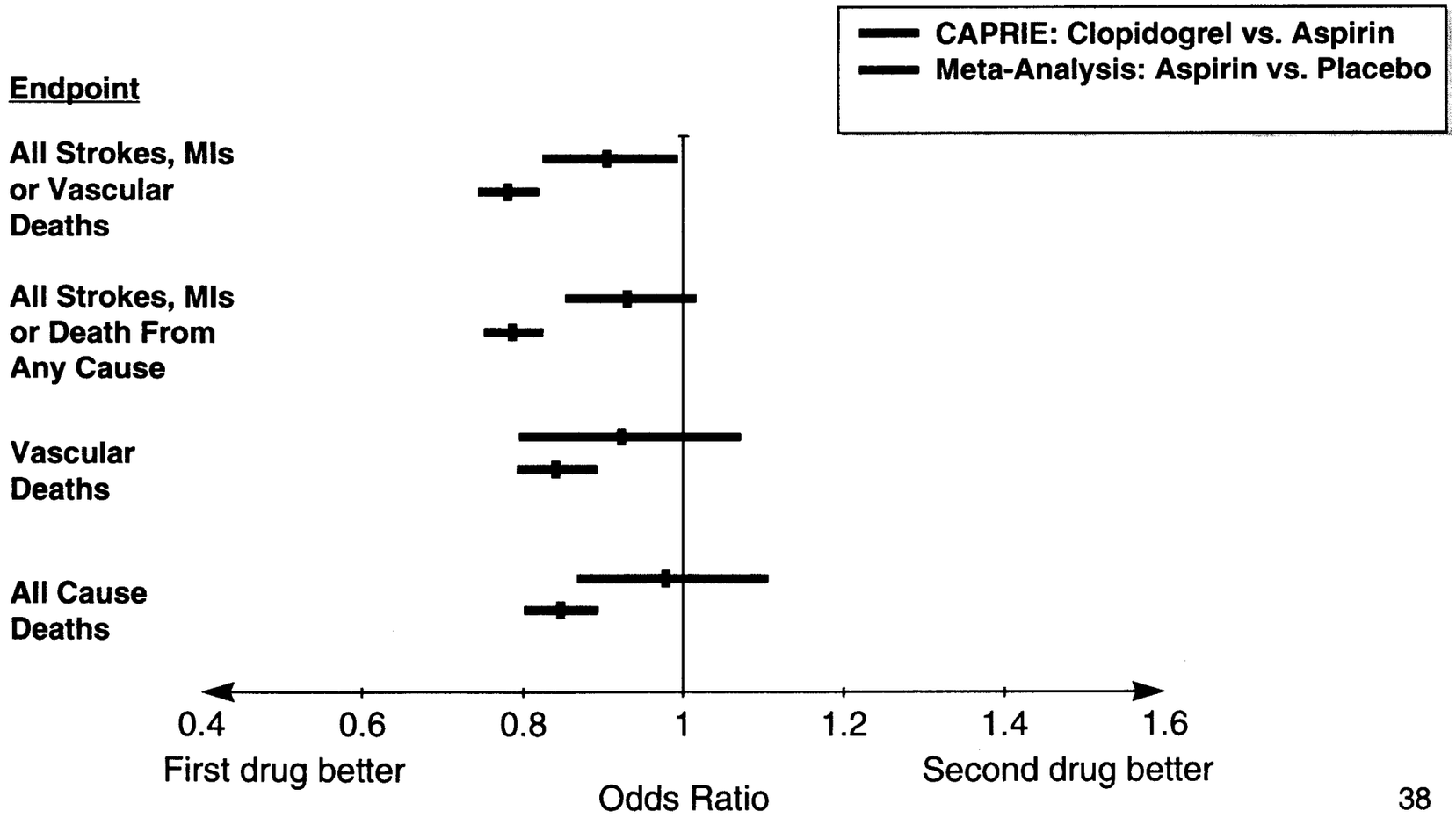

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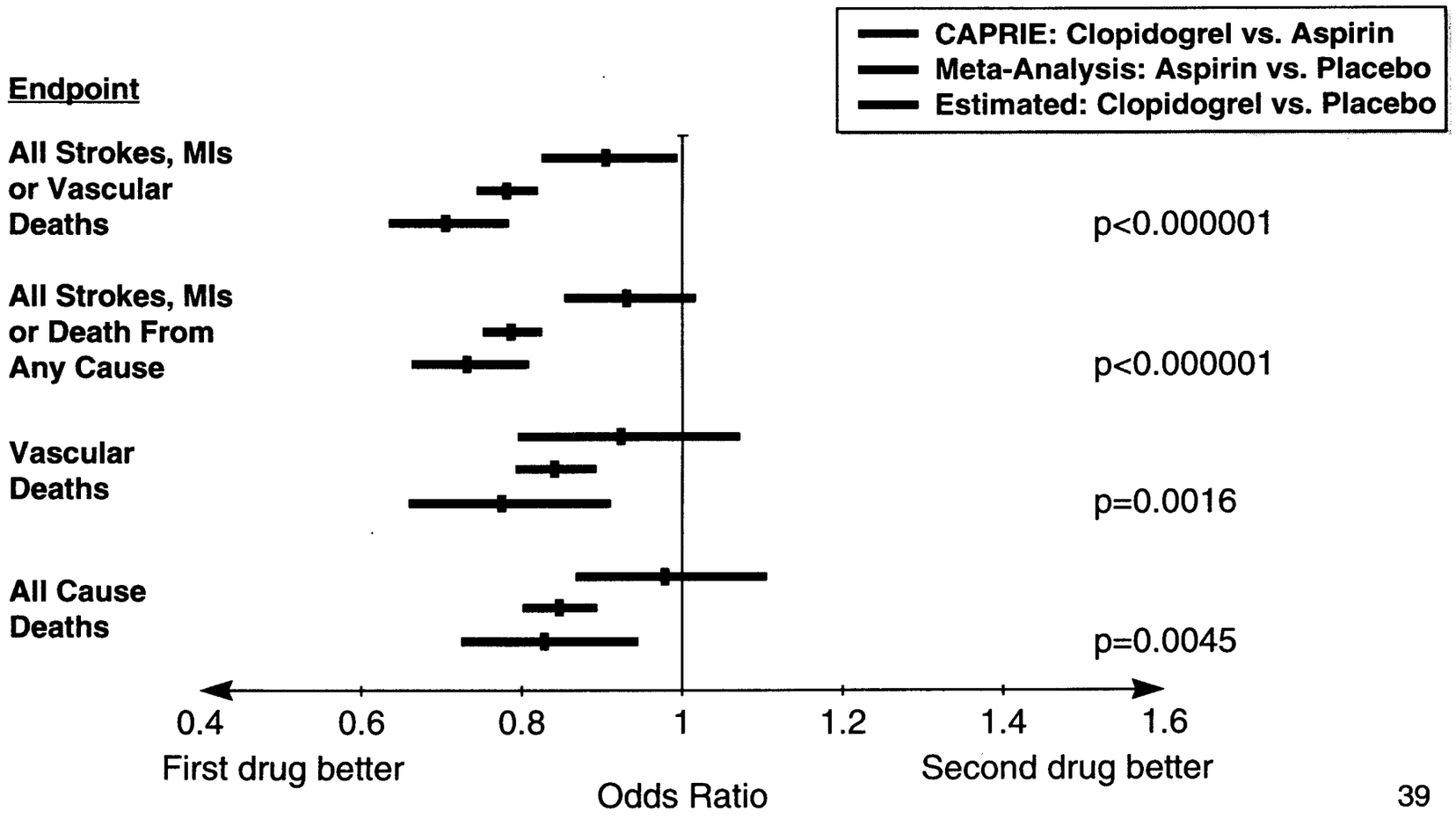
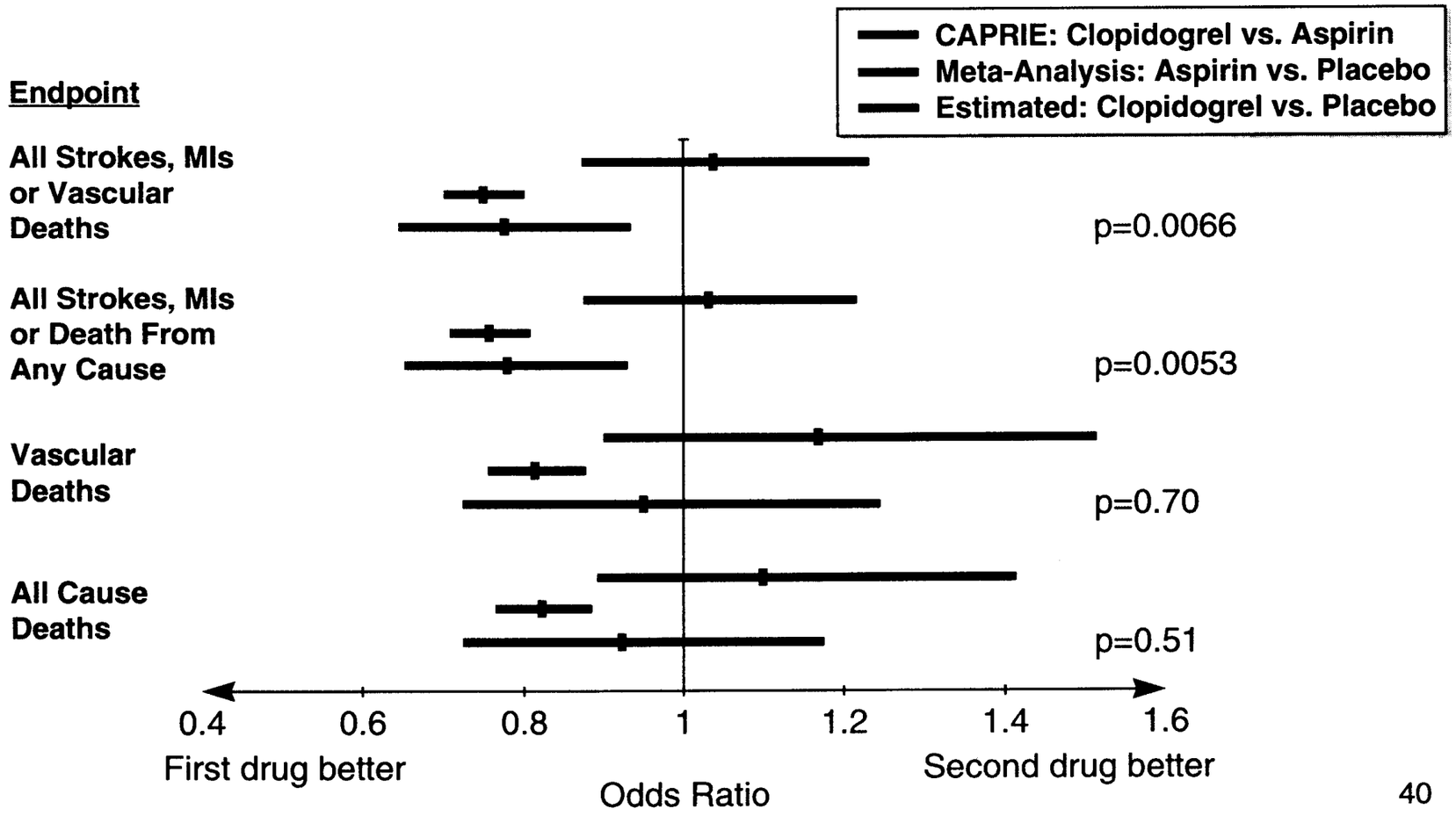
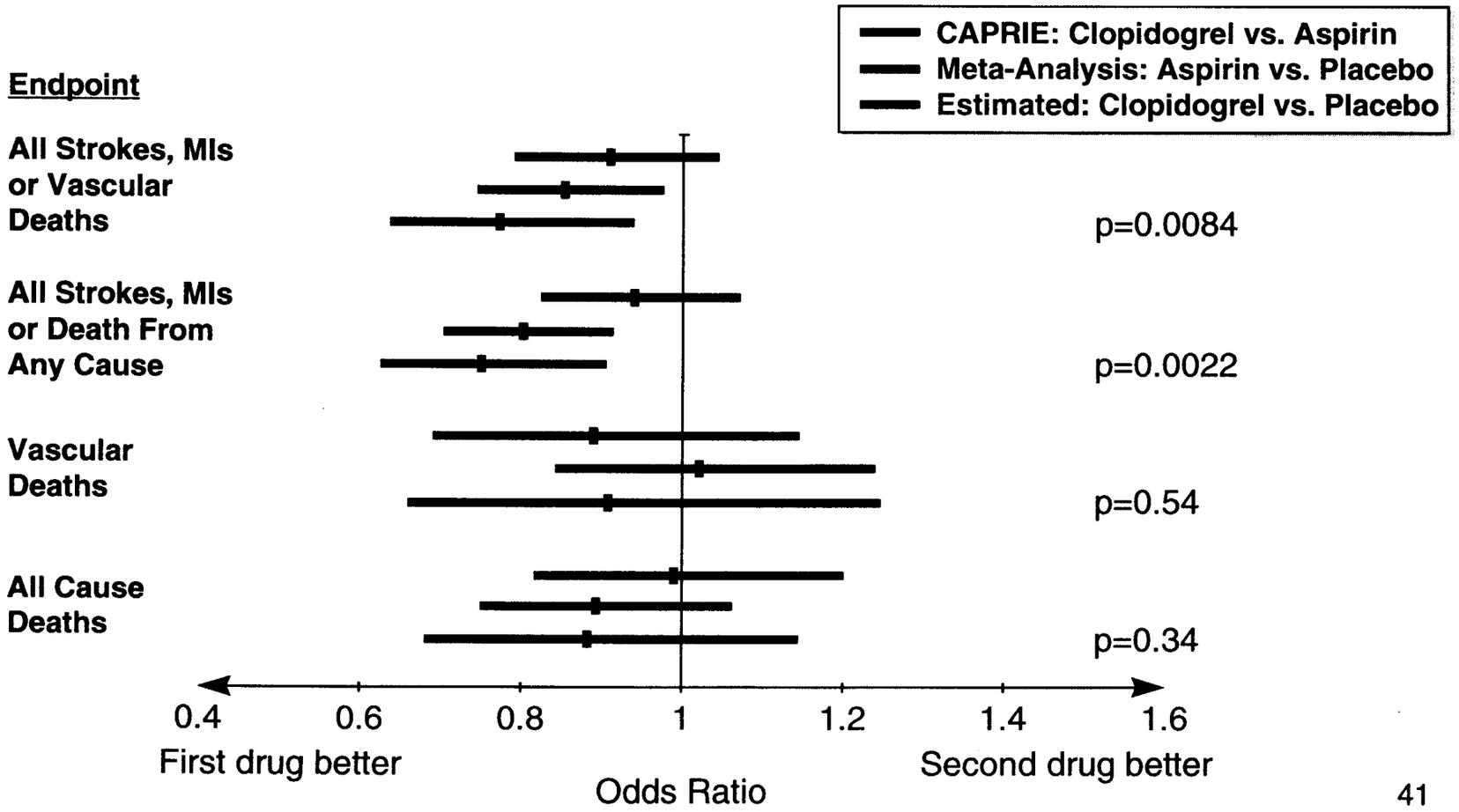


Clopidogrel vs. Synthetic Placebo Control
Odd Ratios and 95% Confidence Intervals
By MI Qualifying Condition



Clopidogrel vs. Synthetic Placebo Control
Odd Ratios and 95% Confidence Intervals
By IS Qualifying Condition



Clopidogrel vs. Placebo in PAD

- Insufficient data (only 17 events) in PAD patients in the meta-analysis to support a formal calculation of clopidogrel's efficacy versus placebo.
- Aspirin is widely used for the prevention of atherothrombotic events in patients with PAD
- Aspirin has a Grade A recommendation from the Fourth Consensus Conference of the American College of Chest Physicians for treatment of patients with PAD
- Clopidogrel was superior to aspirin in the PAD subgroup in the CAPRIE trial.

Two Positive Study Paradigm

- Two controlled trials with two-sided p-values ≤ 0.05 are typical for regulatory approval.
- The probability that two trials satisfy this criterion is $2 \times 0.025 \times 0.025 = 0.00125$.
- In this placebo analysis, clopidogrel clearly satisfies this level of significance ($p<0.000001$).

Conclusion

Comparison with Placebo

- Although the use of historical placebo controls can be problematic, the uniformity of the aspirin effect in the 41 trials of the APTC meta-analysis provided a robust basis for the clopidogrel versus placebo comparison.
- The comparison of clopidogrel versus placebo is highly significant and beats the "two trials at $p \leq 0.05$" paradigm.

Conclusion

Comparison with Placebo

- Clopidogrel is significantly better than placebo for:
  - all stroke / MI / vascular mortality
  - all stroke / MI / all cause mortality
  - vascular mortality
  - all cause mortality
- Clopidogrel is significantly better than placebo in the MI and IS subgroups for:
  - all stroke / MI / vascular mortality
  - all strokes / MI / all cause mortality

Conclusions
Comparison with Placebo

- Clopidogrel meets the usual placebo standard and is superior to aspirin overall.

Statistical Issues

- How would clopidogrel compare with placebo if such a trial were ethical?
- How robust is the observed differential treatment effect by qualifying condition subgroup (called an interaction)?

Possible Treatment Difference by Qualifying Condition

- Multiple comparisons are clearly an issue:
  - Primary outcome cluster - ITT and OT
  - IS, MI, amputation or vascular death - ITT and OT
  - Vascular death - ITT and OT
  - Any stroke, MI or death from any cause - ITT and OT
  - Death from any cause - ITT and OT
  - Cox Proportional Hazards model with adjustment for prognostic factors for all of above
  - Analysis to investigate consistency across geographical subgroups
  - Analysis to investigate consistency across clinical disorders

Possible Treatment Difference by Qualifying Condition

- Estimated probability is 35% that one or more qualifying condition subgroups will show a negative effect by chance.
  - Assuming that the number of events in each of the qualifying condition subgroups was the number actually observed.
  - Assuming the overall odds ratio was the same as the observed overall odds ratio.
  - Assuming the same odds ratio in each qualifying condition subgroup.

Possible Treatment Difference by Qualifying Condition

- Quantitative interaction = positive effect in all subgroups, but possibly different magnitudes. Not usually of much clinical concern.
- Qualitative interaction = positive effect in one or more subgroups; negative effect in one or more subgroups.

Possible Treatment Difference by Qualifying Condition

- Very doubtful there is much of a difference. Even if there is, it is probably a *quantitative interaction* not a *qualitative interaction*.

Conclusions

Possible Treatment Difference by Qualifying Condition

- Statistics are suggestive at best, not conclusive, for a treatment interaction because of large multiple comparison issue.
- Observed interaction is likely quantitative, but not qualitative.
- Negative estimate is well within the realm of chance (35%).

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Clinical Issues

- Does the observed variation in treatment effects across the qualifying condition subgroups make clinical sense?
- What are the clinical implications of treatment with clopidogrel?

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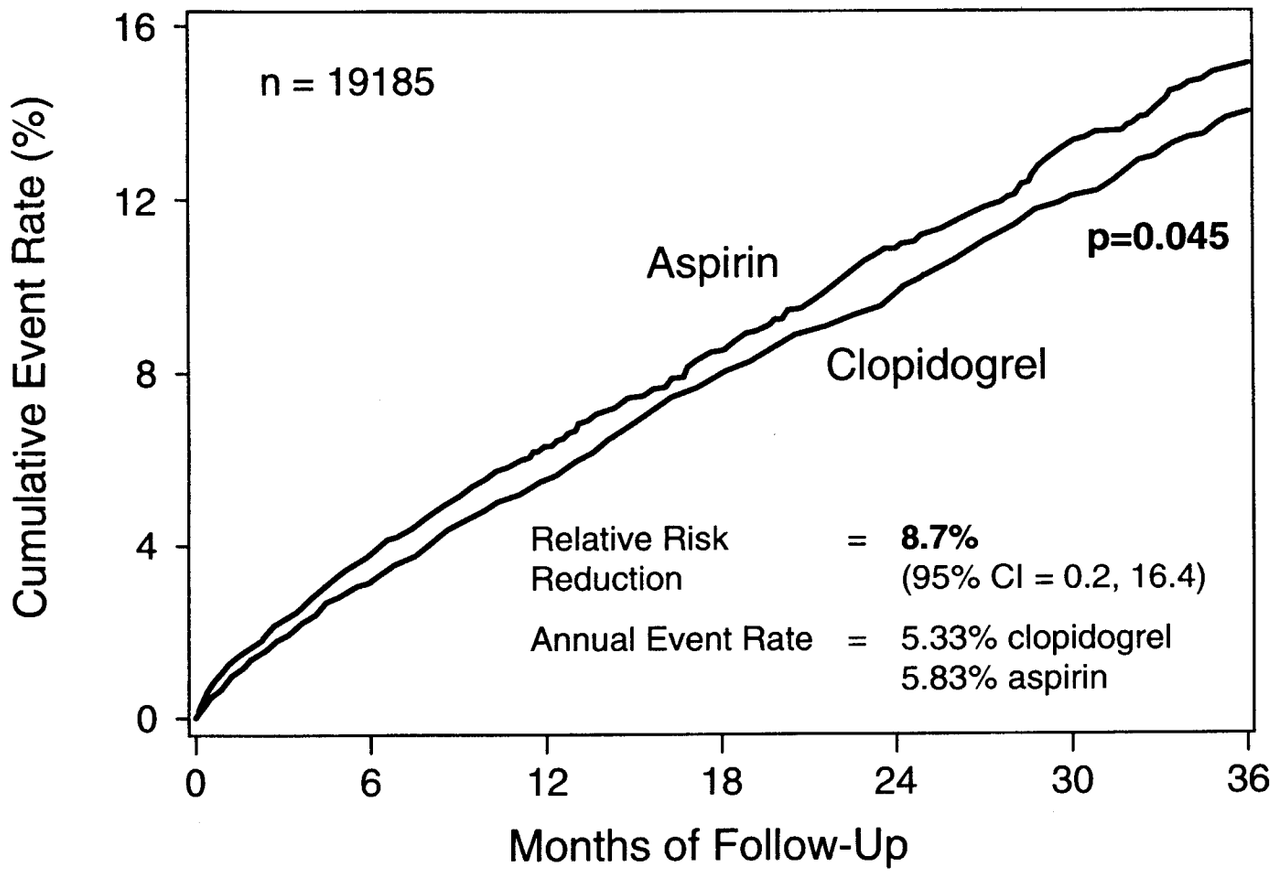
Primary Analysis

IS, MI or Vascular Death



Patients Experiencing MI, IS and Vascular Death During the Study

Outcome Event	No. of Patients Experiencing Event		RRR %
	clopidogrel	aspirin	
IS	450	470	5.2
MI	276	341	19.2
Vascular Death	350	378	7.6

RRR = Relative Risk Reduction

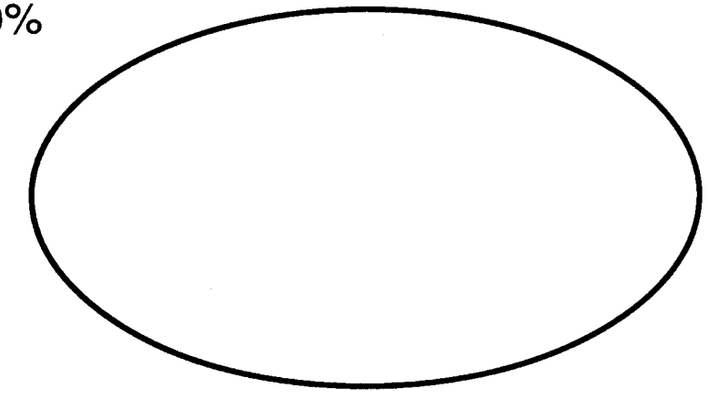
Allocation to Qualifying Condition Subgroups

- Time windows for IS and MI:
  - IS: 1 week to 6 months
  - MI: within 35 days
- No time restriction for PAD
- Atherosclerotic disease in more than one vascular bed was not an exclusion.

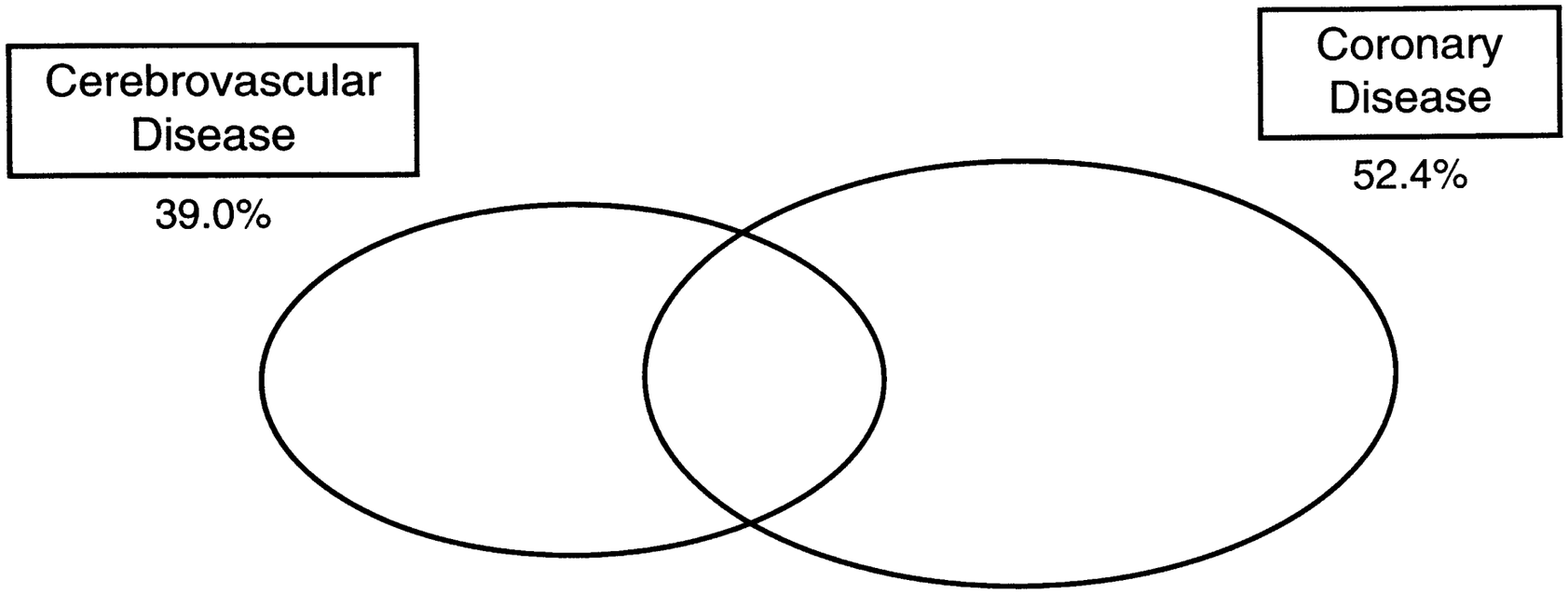
Distribution of Symptomatic Atherosclerosis in the CAPRIE Population

Cerebrovascular Disease

39.0%



Distribution of Symptomatic Atherosclerosis in the CAPRIE Population



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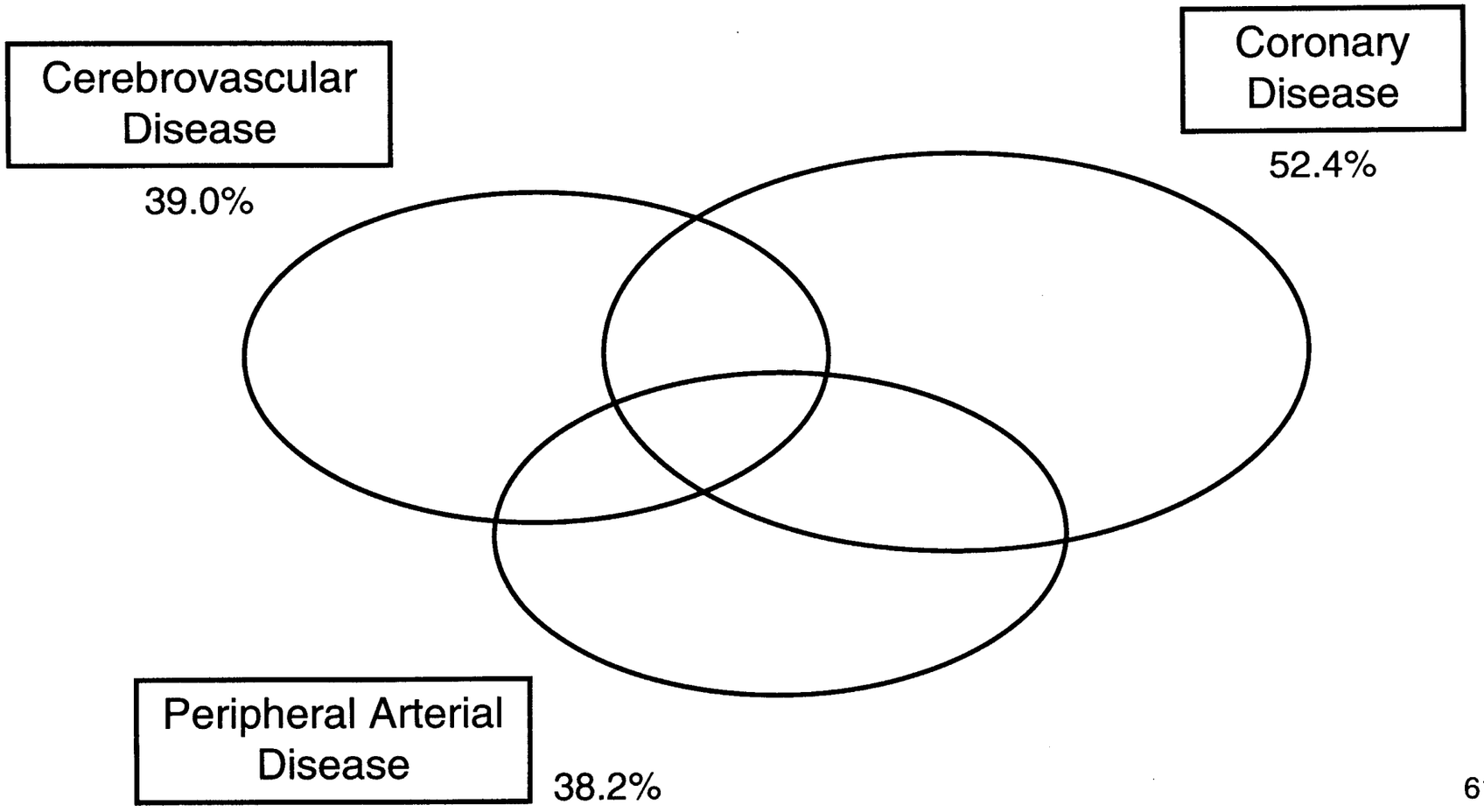

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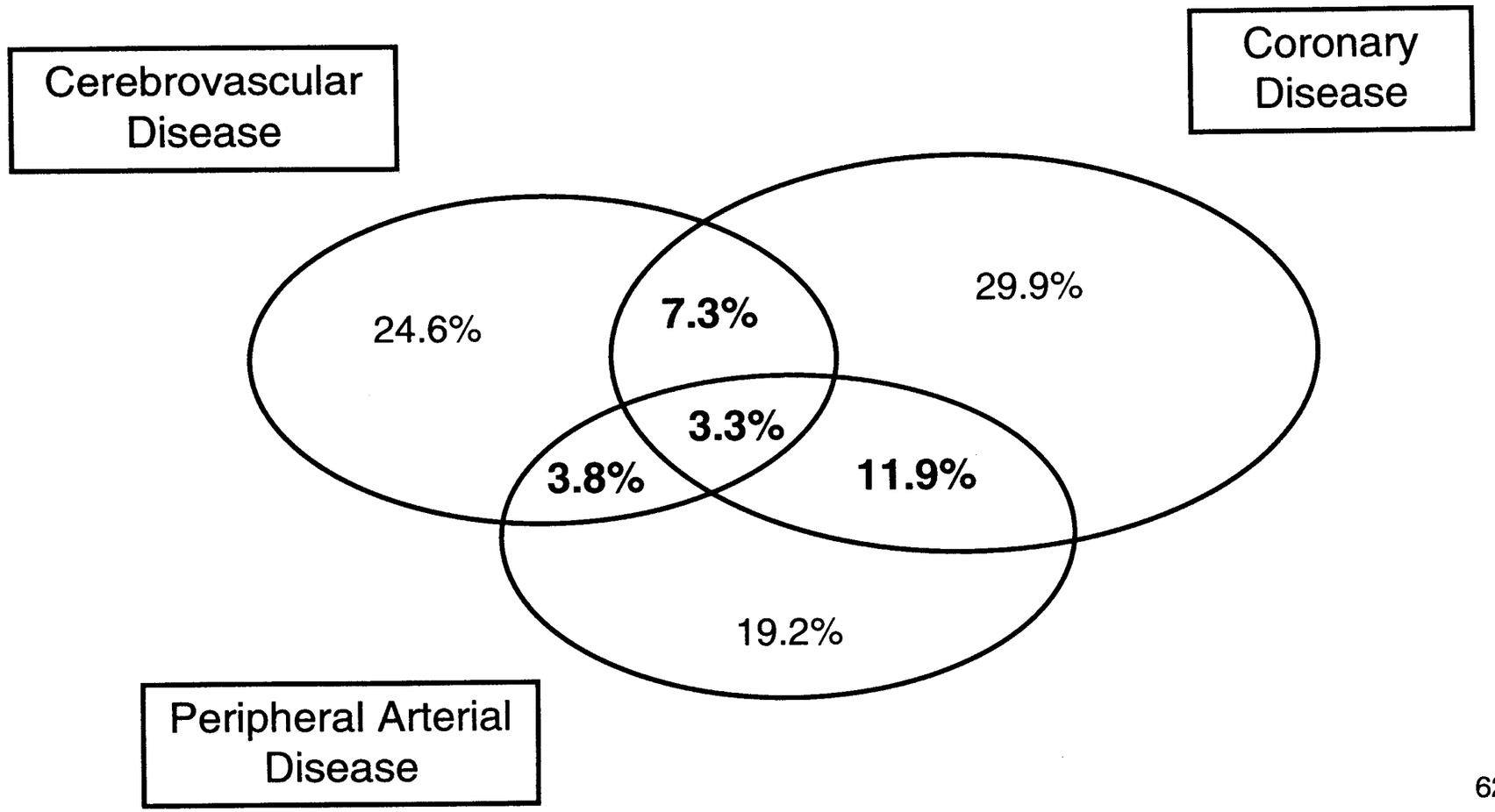
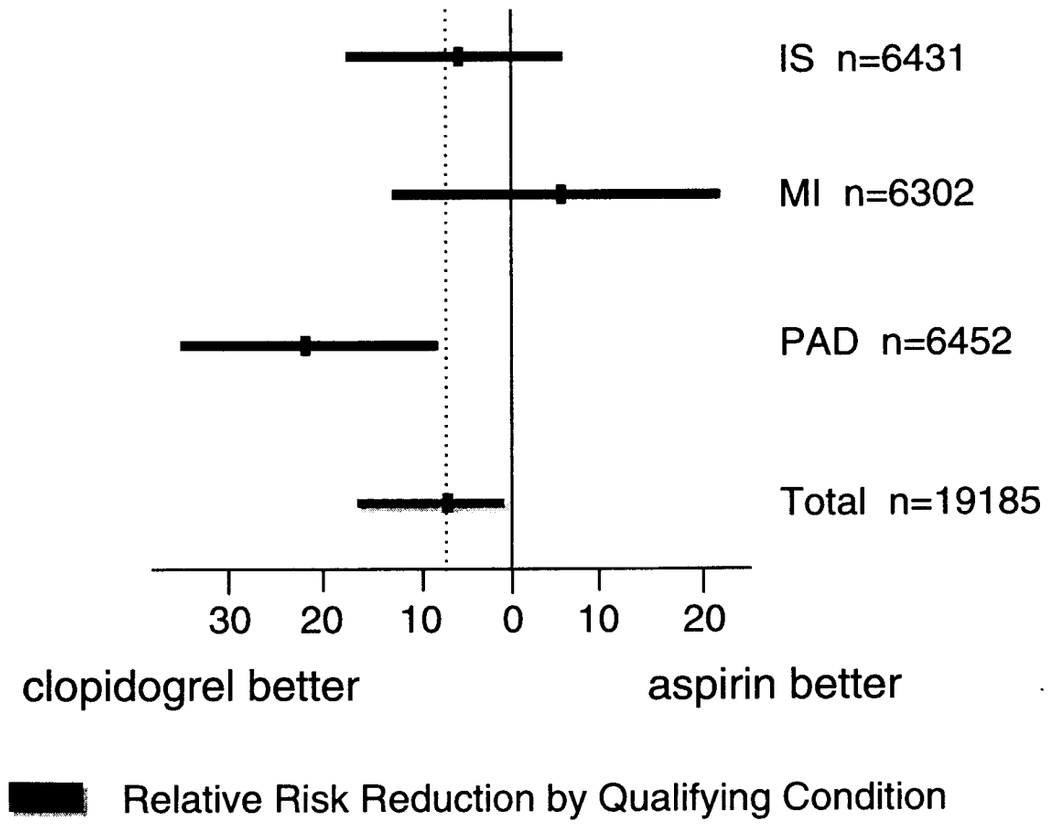
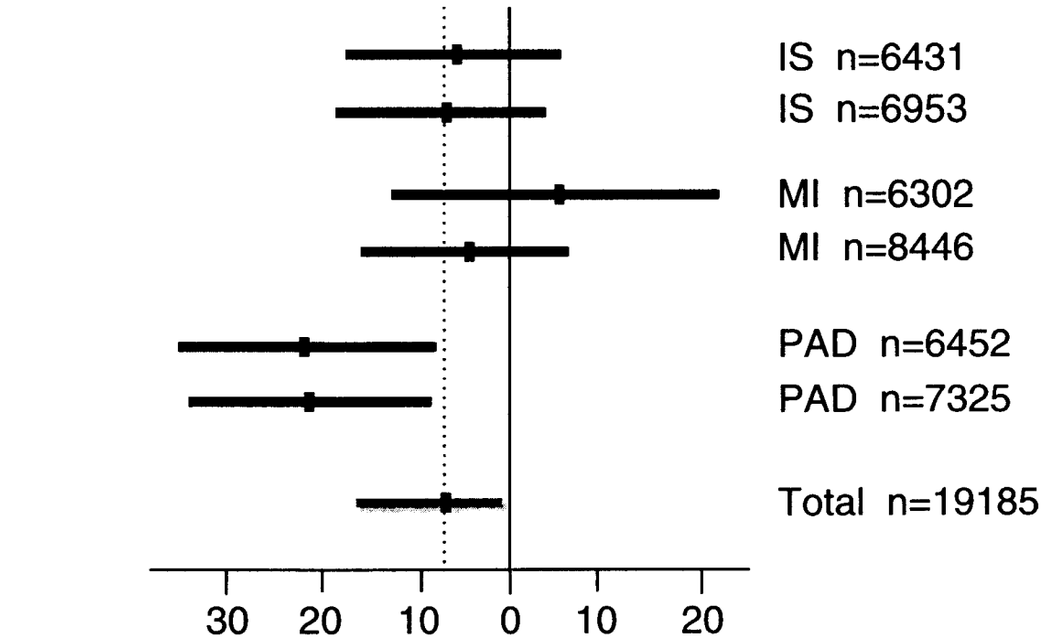


Relative Risk Reduction by Atherosclerotic Condition



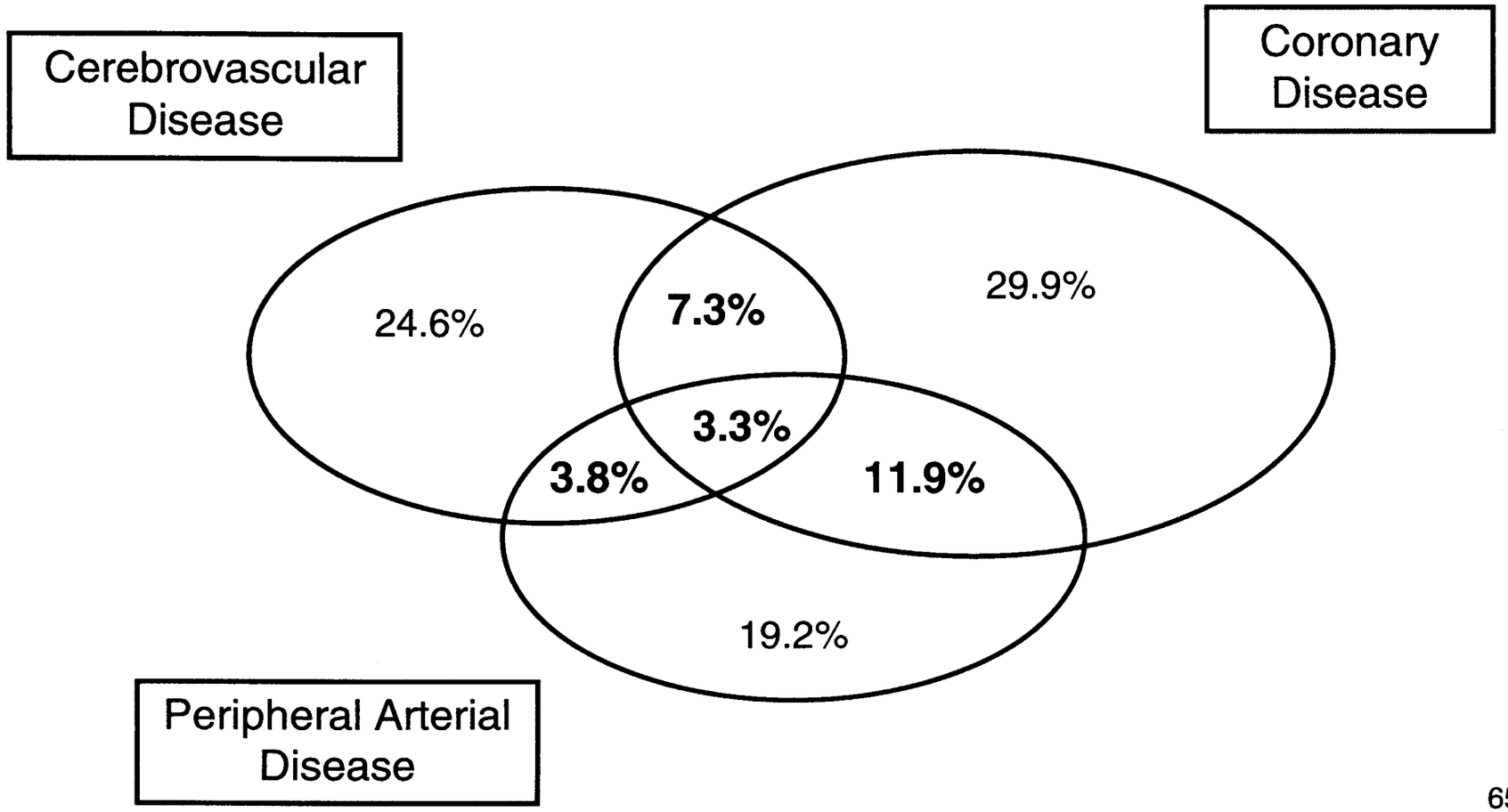
Relative Risk Reduction by Atherosclerotic Condition



Relative Risk Reduction by Qualifying Condition

Relative Risk Reduction by Any History (including QC)

Distribution of Symptomatic Atherosclerosis in the CAPRIE Population



Disease Burden

Primary outcome cluster (IS, MI or vascular death)

Disease History	No. of Patients	RRR % (95% CI)
PAD only	3677	17.0 (-12.1, 38.6)
Coronary disease only	5729	0.4 (-19.6, 17.1)
Cerebrovascular disease only	4726	5.5 (-11.7, 20.0)
PAD - any history	7325	22.4 (9.8, 33.3)
Coronary disease - any history	10047	7.6 (-3.8, 17.8)
Cerebrovascular disease - any history	7503	8.3 (-3.5, 18.8)
Disease in two or more beds	5053	14.8 (1.9, 26.0)

RRR = Relative Risk Reduction

Conclusions

- Qualifying condition criteria driven mainly by trial design considerations
- Considerable overlap in medical history between the subgroups
- Greater convergence of treatment effects when overall medical condition of the patients is taken into account

Conclusions

- Clopidogrel reduces the percentage of patients experiencing ischemic stroke, myocardial infarction or vascular death
- Most marked effect is reduction in fatal and nonfatal MI
- Clinically compelling to expect this benefit in the group with past MI at entry
- Observed subgroup treatment differences lack clinical credibility

Clinical Issues

- Does the observed variation in treatment effects across the qualifying condition subgroups make clinical sense?
- What are the clinical implications of treatment with clopidogrel?

Primary Analysis

Primary Outcome Cluster	No. of Patients with Events		RRR % (95% CI)	p-Value
	clopidogrel n=9599	aspirin n=9586		
IS, MI, or Vascular Death	939	1020	8.7 (0.2, 16.4)	0.045

- Fatal or potentially disabling events
- Pre-defined definitions for validation
- Blinded validation by at least two adjudicators
- Final decision by entire CVC if disagreement

RRR = Relative Risk Reduction

Absolute Risk Reduction

Event rate for primary outcome cluster

	Annual Event Rate %		
	Clopidogrel n=9599	Aspirin n=9586	Risk Reduction
IS, MI or Vascular Death	5.33	5.83	0.5%

- Clopidogrel prevented 5 additional events per 1000 patient-years of treatment.
- Aspirin would be expected to prevent 19 events per 1000 patient-years of treatment and clopidogrel 24 events.

Absolute Risk Reduction

		Relative Risk Reduction	Event Rate / Yr per 100	Events Saved / Yr per 1000
Antiplatelet Trialists' Collaboration	control	25 %	7.77	19
	aspirin		5.83	
CAPRIE		8.7 %		24
	clopidogrel		5.33	

Clinical Impact of Clopidogrel

- To prevent 1 potentially fatal or disabling event each year in patients with symptomatic atherosclerosis:
  - treat 42 patients with clopidogrel
  - treat 53 patients with aspirin
- The benefits of clopidogrel therapy are comparable to those of other interventions in high risk patients

Net Benefit Cluster

Outcome	No. of Patients with Events		RRR % (95% CI)	p-Value
	clopidogrel n=9599	aspirin n=9586		
Any Stroke, MI, Vascular Death, or Hemorrhagic Death	970	1062	9.4 (1.2, 17.0)	0.025

RRR = Relative Risk Reduction

Conclusions

- The superior efficacy of clopidogrel in the prevention of vascular events is both statistically significant and clinically meaningful.

- In addition to this superior efficacy there is a reduced risk of severe hemorrhagic events compared with aspirin.

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Summary

- We have established the superiority of clopidogrel to aspirin. The CAPRIE study results consistently confirm this superiority.
- Overall, clopidogrel is at least as safe as aspirin, with significantly less GI bleeding.
- A comparison of CAPRIE and APT data (clopidogrel, aspirin and placebo) provides a high degree of confidence that clopidogrel would have been superior to placebo in a direct comparison.

Summary

- The differential treatment effect observed across the three qualifying conditions is neither statistically nor clinically compelling.
- Because of the generalized nature of atherosclerotic disease, the benefits of clopidogrel may be expected across this entire patient population.

Summary

- Clopidogrel is safe and effective in the prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease.