Br. J. clin. Pharmac. (1984), **17**, 703–711

Low-dose acetylsalicylic acid (100 mg/day) after aortocoronary bypass surgery: a placebo-controlled trial

W. MEISTER, C. v. SCHACKY, M. WEBER, R. LORENZ, J. KOTZUR, B. REICHART[1], K. THEISEN & P. C. WEBER.
Medizinische Klinik Innenstadt, University of Munich, and [1]Herzchirurgische Klinik, University of Munich, Munich, F.R.G.

1 The effect of low-dose acetylsalicylic acid (100 mg/day) upon bypass patency-rate and clinical course after aortocoronary bypass surgery was investigated in a randomized, placebo-controlled clinical trial.
2 Sixty patients with 143 distal anastomoses of bypasses were randomized, 46 underwent repeat angiography after 4 months.
3 Using the intention to treat-strategy, treatment was superior to placebo as judged by bypass patency rate and occurrence of cardiovascular complications or death. Counting the six drop-outs as failures, only nine of the 31 patients of the placebo group, but 16 of the 29 patients of the treatment group were considered successes ($P < 0.04$).
4 Eighteen patients in the placebo group and eight patients of the treatment group received β-adrenoceptor blockers postoperatively, suggesting again a favourable effect of the treatment.
5 Adverse drug reactions were very rare and minor.
6 Supported by pathophysiological insights and positive trends in similar trials, the positive result justifies the recommendation of prescribing 100 mg of acetylsalicylic acid once daily to all patients without contraindications after aortocoronary bypass surgery.
7 The positive result of this trial warrants further clinical trials of low-dose acetylsalicylic acid for other indications in arterial diseases.

Keywords acetylsalicylic acid coronary artery bypass

Introduction

Platelets play a central role in the pathogenesis of arteriosclerotic and arteriothrombotic diseases. Therefore, antiplatelet agents should be an effective treatment for these conditions.

Recent experimental evidence and a clinical trial suggest that low-dose acetylsalicylic acid (ASA) may be a very potent and clinically useful antiplatelet agent (O'Grady & Moncada, 1978; Harter *et al.*, 1979; Hanley *et al.*, 1981; Moncada, 1982; Weksler *et al.*, 1983). Irrespective of the proposed and disputed higher efficacy, a low dose should in any case carry a smaller risk of adverse drug reactions than a conventional dose of ASA (Majerus, 1983; Marcus, 1983).

A clinical model for evaluating a prophylactic therapy should provide a reliable assessment of a not too infrequent event in a reasonable time. We decided to test the efficacy of low-dose acetylsalicylic acid (ASA) for enhancing bypass patency rate in the first 4 months after aortocoronary bypass surgery. Our trial was conceived as a randomized, placebo-controlled trial with

the predetermined endpoints angiographically demonstrated bypass occlusion or cardiovascular complications.

During the course of our trial, the positive result of another trial was published (Chesebro *et al.*, 1982). An earlier interim analysis of our results had disclosed a favourable trend for the active drug. Since further placebo administration was deemed unethical, new patients were no longer recruited and the final trial size was smaller than planned. Nevertheless, a favourable effect of the active drug was found. We conclude, that low-dose ASA is an effective antiplatelet agent.

Methods

The trial was approved by the ethics committee of the Medical Faculty of the University of Munich.

All patients from our hospital scheduled for aortocoronary bypass surgery were considered for participation. Exclusion criteria were: gastrointestinal ulcer disease, asthma bronchiale, haemorrhagic diathesis, indications for antiphlogistic, analgesic or anticoagulant medication, stroke, advanced diabetes mellitus or other serious concomitant disease. Patients were asked for informed consent prior to surgery and were randomized and started on the study-medication at 14.00 h the day after surgery.

Randomization using a random number table was performed in three strata: first, presence of advanced coronary heart disease (ventricular arrhythmias Lown grade IV, ventricular ejection fraction smaller than 40%), second, acute myocardial infarction in the six months prior to operation, and third, unfavourable bypass conditions or a complicated perioperative course (thrombendarterectomy, a bypass-flow of less than 30 ml/min, stenosis distal to the anastomosis or postoperative hypotension; a bypass-flow of more than 100 ml/min compensated for one of the aforesaid conditions).

Coronary arteriography is currently recommended by us to all patients with known or suspected coronary heart disease independent from the severity of their symptoms. From May 1980 through June 1982 coronary artery bypass surgery was suggested to a consecutive series of 101 patients after coronary arteriography. The process leading finally to the randomized 60 patients (31 in the placebo and 29 in the ASA group) is summarized in Figure 1.

Before, 2–3 weeks after surgery, and at the end of the individual observation period (scheduled at 4 months after surgery) the following data were collected: history (especially cardiac symptoms, medications, adverse drug reactions), clinical examination, standard 12-lead ECG, routine laboratory examination, and platelet function tests (Lorenz *et al.*, 1983). Coronary arteriography and left ventricle angiography were performed before and at the end of the trial.

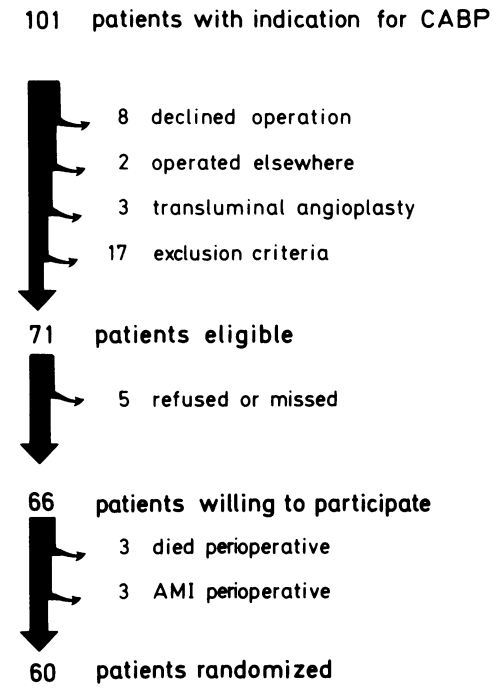

Figure 1 Summary of the selection process, leading from a continuous series of 101 patients with indication for coronary artery bypass surgery (CABP) to 60 patients finally randomized. AMI: patients with acute myocardial infarction.

The predetermined clinical endpoints of the study were: events typical for a deleterious course of coronary heart disease (myocardial infarction, unstable angina pectoris, sudden death), as well as other cardiovascular complications of a thromboembolic nature.

To assess compliance, we interviewed the patients, counted the pills, and measured the pharmacodynamic effect of ASA (i.e. the platelet function). The study medication was administered as a single tablet to be taken with breakfast. The matching tablets (100 mg ASA or placebo) were dispensed in blister packs with 30 tablets per unit (provided by Bayer AG, FRG).

Blindness in the trial was threatened especially by conducting thrombocyte function studies. Strict separation of the laboratory group from the clinical group was the only possible way to ensure blindness, since special blood collection routines and immediate assaying were necessary.

For statistical analysis, the Fisher exact test and a modified Chi square test (see appendix) were applied to assess the outcomes. Baseline values were compared by the *t*-test for unpaired samples unless visual inspection of the data suggested the use of the nonparametric Wilcoxon-U-test. Sample size estimation assumed the following numbers: $\alpha < 0.05$ (two-tailed), $\beta < 0.20$, and an increase in bypass patency rate from 70 to 85%. A trial size of 146 cases was predicted (Fleiss, 1973).

Results

The two groups were equal in most of the baseline values: they did not differ in respect to age (55 years on the average; the first figure in this and the following parentheses refers to the placebo group, the second to the ASA group), weight (104 *vs* 107% of norm on the average (height in cm-100) in kg)), sex (28 males and three females *vs* 24 males and five females), previous myocardial infarction (24 *vs* 17 patients), occurrence of spontaneous angina pectoris (15 *vs* 11 patients), history of smoking (23 *vs* 17 patients), hyperlipidaemia (19 *vs* 12 patients), hypertension (six *vs* six patients), number of angiographically demonstrated stenosed vessels (2.77 *vs* 2.76 on the average), or occurrence of Lown grade IV ventricular arrhythmias (four *vs* nine patients). Inequalities occurred in respect to the angiographically determined ejection fraction and the number of anastomoses performed during surgery (Table 1).

Table 2 summarizes the time and nature of the observed clinical trial endpoints.

Two patients in the placebo group and four patients in the ASA group refused repeat angiography, reported to be well, and were considered drop-outs.

Forty-six patients underwent repeat angiography (on the average 129 and 131 days after surgery in the placebo and the ASA group, respectively). The results (Table 3) show significant differences in favour of the ASA group.

The additional medication changed substantially during the trial (Table 4). β-adrenoceptor blocking agents were prescribed significantly less frequently in the ASA group at trial end, whereas no such difference existed at the time prior to surgery. This difference suggests a better functional status in the ASA group, since the change in the severity of the angina pectoris did not differ in both groups: 18 patients in the placebo and 16 patients in the ASA group reported an unequivocal improvement of their anginal syndrome. Unfortunately objective measures of the functional status were not part of the protocol.

Routine electrocardiography disclosed two cases of late postoperative myocardial infarction in the ASA group.

In order to analyze the trial by the intention to treat-strategy, two contrasts were constructed based on the results as shown on Figure 2. Patients with all bypasses patent at repeat angiography were considered 'successes', patients having at least one bypass closed or having reached a clinical endpoint 'failures'. In contrast A, the drop-outs (all had reported to be well), were added to the 'successes'; in contrast B, however, the worst case was assumed and all drop-outs were added to the 'failures'. A significant result was obtained for both contrasts (Table 5).

Our attempts to measure compliance revealed only two non-compliers: one patient of the ASA group did not show inhibited aggregability of his platelets (he dropped out later on) and a patient of the placebo group started to take antiplatelet medication. On the other hand, our methods fall short of ascertaining compliance over the entire trial period. Counting pills or asking patients is notoriously unreliable and the pharmacodynamic control would turn positive by a single tablet taken 1— or even 7—days before admission.

Adverse drug reactions were very rare and minor. Special attention was given to potential early postoperative bleeding in the ASA group, but neither red cell counts nor blood loss through thorax drains nor units of volume replaced differed between the two groups. The following late adverse effects were reported upon specific questioning: Increased bleeding after minor

Table 1 Unequal baseline characteristics

	Placebo *mean*	*(n = 31)* (s.d.)	*ASA* *mean*	*(n = 29)* (s.d.)	P*
Ejection fraction (%)	55	(13)	61	(9)	0.04
Distal anastomoses/patient	3.35	(0.92)	2.69	(1.07)	0.01
Proximal anastomoses/patient	2.23	(0.56)	1.90	(0.77)	0.06

* Student's *t*-test

Table 2 Cardiovascular complications

Trial day	*Group*	*Clinical event*
2	placebo	stroke (died)
6	placebo	acute myocardial infarction (died)
4 + 13	placebo	acute myocardial infarction and stroke
27	placebo	pelvic vein thrombosis
30	placebo	pulmonary embolism
2	ASA	acute myocardial infarction (died)
30	ASA	crescendo angina
95	ASA	sudden death

Table 3 Angiographic results

	Placebo	*ASA*	*P* (F)	*P* (mChi)
Patent distal anastomoses	53/81	46/57	0.04	0.08
Patent proximal anastomoses	36/53	36/40	0.01	0.02
Patients with all anastomoses patent	9/24	16/22	0.02	

P (F): α error using Fisher exact test
P (mChi): α error using modified Chi square test

injuries by a patient of each group, increased menstrual bleeding by a patient in the ASA group, and gastric discomfort by a patient in the ASA group. None of the patients withdrew. Routine laboratory examinations including haemoglobin, erythrocyte count and haematocrit, did not indicate any adverse drug reactions.

Discussion

Our trial suggests a favourable effect of 100 mg per day of acetylsalicylic acid (ASA) upon the postoperative course after coronary artery bypass surgery as judged by the angiographically determined bypass patency rate (Table 3), the need for β-adrenoceptor blocking agents (Table 4), or the overall therapeutic success rate combining angiographic results and clinical events (Table 5).

Bypass patency is one of the major determinants of prognosis in patients after aortocoronary bypass surgery (Bourassa *et al.*, 1973; Mundth & Austen, 1975; Hartman *et al.*, 1977; Campeau *et al.*, 1976; Aşsad-Morell *et al.*, 1980). Earlier trials of anticoagulant or antiplatelet agents after aortocoronary bypass surgery did not yield conclusive positive results (Pantely *et al.*, 1979; Maycr *et al.*, 1980; Gohlke *et al.*, 1981; Baur *et al.*, 1982; McEnany *et al.* 1982; Sharmà *et al.*, 1983). A convincing report was recently published by Chesebro *et al.* (1982) and prompted us to close our trial. A regimen of dipyridamole and

Table 4 Change in medication

	Placebo (n = *24*)		*ASA* (n = *22*)		
	pre	*post*	*pre*	*post*	P*
Long-acting nitrates	21	8	22	6	
β-adrencoeptor blocking agents	22	18	20	8	0.01
Digitalis glycosides	4	10	4	9	
Diuretics	5	8	4	4	
Antiarrhythmics	2	5	2	2	

pre: number of patients receiving drug at preoperative evaluation
post: number of patients receiving drug at repeat angiography
*: Fisher exact test

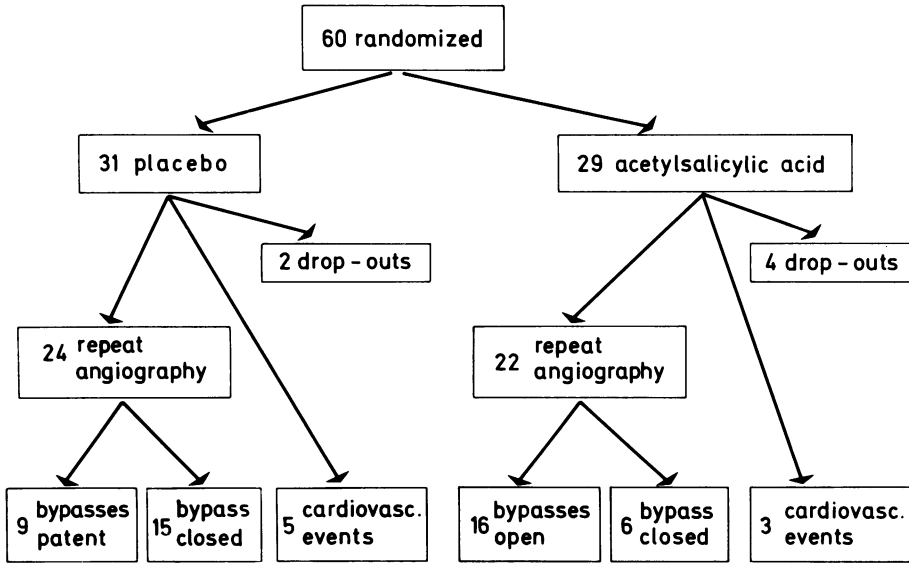

Figure 2 Summary of the results of the trial including all patients originally randomized. Numbers refer to number of patients. Results of repeat angiography refer to the dichotomy 'patient with all bypasses patent' or 'patient with one or more bypasses closed'. The cardiovascular events are those counted as trial endpoints (see Table 2 for further details).

1000 mg ASA/day started as early as 7 h postoperatively after preoperative pretreatment with dipyridamole significantly increased the bypass patency rate after 7 days to 6 months as compared to placebo.

Figure 3 summarizes the findings of earlier trials. For comparison, our result is included. In our opinion, the earlier trials indicate the potential of antiplatelet (or possibly anticoagulant) therapy to improve bypass patency, but they suffer from methodological deficiencies. Most importantly, clinical end-points were neglected and—even more important—an analysis using the intention to treat-strategy (i.e. the pragmatic or management analysis (Sackett & Gent, 1979; Hampton, 1981)), was never used. Another important pitfall for clinical trials is the substitution of so-called hard (but potentially irrelevant) data for so-called soft (but clinically relevant) data (Feinstein, 1977). Focusing upon angiographically demonstrated bypass patency, the earlier trials weaken their conclusions on account of both problems.

Table 5 Number of successes

	Placebo (n = *31*)	*ASA* (n = *29*)	P*
Contrast A	11	20	0.01
Contrast B	9	16	0.04

*Fisher exact test

Furthermore, a low fraction of patients finally entering randomization, like the 22% in the trial of Chesebro *et al.* (1982), remains discomforting. In our trial, 60% of all patients considered for participation were randomized and the selection process is fully described (see also Figure 1).

Three problems question the relevance of our results: the small trial size, the relatively low patency rate in the placebo group, and inequalities in the base-line characteristics of the two groups.

Sample size estimation predicted 146 cases per group. Whether a case means a bypass (or an anastomosis) or a patient is open to discussion. Many factors have been reported to increase the risk of bypass occlusion (Mundth & Austen, 1975; Campeau *et al.*, 1977). If one stresses individual factors operating in the patient like platelet function, hypotension, or severity of disease, a case must be a patient. If one stresses local factors operating at the anastomosis like endothelial damage, flow turbulence or poor flow, a case must be a distal anastomosis. This latter view would lead to an estimated size of approximately 50 patients per group, assuming an average of 3 distal anastomoses per patient. Our trial, however, was terminated prematurely, when only 29 and 31 patients per group had been randomized. Small trials are at risk to miss a clinical relevant difference (Freiman *et al.*, 1978). Fortunately, our result is a difference. A principally mistrustful attitude towards small

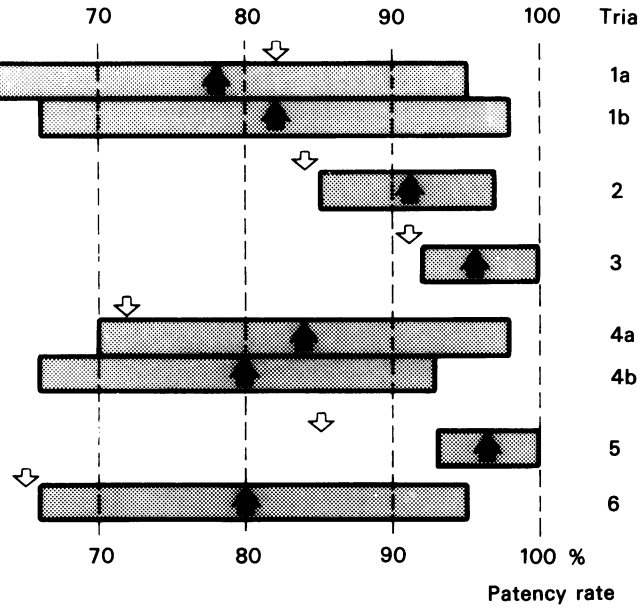

Figure 3 Comparison of the results of trials investigating anticoagulant or antiplatelet therapy after aortocoronary bypass surgery. Open arrows signify patency rate of distal anastomoses in the 'control' group, filled arrows the respective rate in the 'treatment group, the shaded bar the 95% confidence interval of the treatment effect. Results of the following trials were used: Pantely *et al.* (1979) (1a Dipyridamole + ASA, 1b warfarin); Gohlke *et al.* (1981) (2); Baur *et al.* (1982) (3), McEnany *et al.* (1982) (4a warfarin, 4b ASA), Chesebro *et al.* (1983) (5), this trial (6).

trials is not justified; the relevance of a trial showing a difference should not be determined by its size, but by its internal and external validity.

Patency rate in the placebo group was low in our trial compared to that of other published trials: 69% as compared to 72–91% in the other trials. There are no obvious explanations for this variability like differences in exclusion criteria or in follow-up periods. Our experience prior to this trial showed a bypass patency rate of 71% in patients without anticoagulant or antiplatelet therapy (Weber *et al.*, 1982). It is therefore unlikely that the patients in our treatment group had a markedly different risk of bypass occlusion than those in the placebo group. Excluding this type of potential bias, the basic result of our trial, i.e. the efficacy of ASA, need not be questioned. The generalizability of our results, however, may be weakened by this circumstance.

Randomization did not lead to completely equal base-line characteristics of the groups, especially the average number of distal anastomoses per patient was different (3.35 in the placebo *vs* 2.69 in the ASA group). To correct for this confounding variable, the method by Woolf was chosen (see appendix); the α error for accepting a difference between the groups remained low, 0.08 in respect to distal and 0.02 in respect to proximal anastomoses (Table 3). Application of this method to the other contrasts was obviated by the small numbers in the emerging subgroups. From the results for anastomoses we conclude, that this baseline discrepancy probably exerts only a minor influence upon the trial outcome and that the overall interpretation stays the same.

The clinical relevance of this trial, however, depends not only upon the weighing of its advantages and disadvantages, but also upon any other evidence favouring antiplatelet therapy in this situation and upon the clinical utilities of competing therapeutic regimens (including the no-therapy option) (Cox, 1982).

On a biochemical level, ASA inhibits the enzyme cyclooxygenase. This enzyme catalyzes the production of thromboxane A_2, a vasoconstricting and pro-aggregatory substance, in the platelet, but also the production of epoprostenol (PGI_2), a vasodilating and anti-aggregatory substance, in the vascular endothelial cell. The effective inhibition of thromboxane A_2 production and thus of platelet function can be achieved at lower concentrations of ASA than the inhibition of the PGI_2 production in the endothelial cell, since the platelet cannot replace

the acetylated enzyme. Therefore, the use of low rather than high, i.e. conventional doses of ASA has been suggested and experimentally tested as an elegant method to preferentially inhibit the platelets (O'Grady & Moncada, 1978; Hanley *et al.*, 1981; Lorenz *et al.*, 1981; Weksler *et al.*, 1983).

These pathophysiological considerations, the successful use of low-dose ASA in a dose of 160 mg once daily for the prevention of thrombosis of haemodialysis shunts (Harter *et al.*, 1979) and in a dose of 324 mg once daily in unstable angina (Lewis *et al.*, 1983), and the corroborative results of trials with other antithrombotic regimens after aortocoronary bypass surgery (Figure 2) support the case in favour of low-dose ASA therapy. However, the benefit-risk ratios of alternative regimens (especially low-dose ASA versus the combination of dipyridamole plus ASA versus early heparin and succeeding oral anticoagulants) cannot be properly compared using the currently available data. On the risk side, low-dose ASA seems to be superior. High-dose ASA has a substantial risk of bothering adverse effects (Porter & Jick, 1977; Vanecek, 1980), including dyspepsia, nausea, or even vomiting in 10–20% of the patients (Anonymous, 1980) and the risks of an effective oral anticoagulant therapy are well-known albeit their magnitude is a controversial subject for decades. In contrast, low-dose ASA was safe and very well tolerated in our as well as in other trials, although this issue needs to be scrutinized in a much larger group of patients. On the benefit side, not even a vague guess is possible; the alternative regimens were never compared directly and an indirect comparison is obviated by the marked difference in design and conduct of the trials.

Antiplatelet therapy should start as soon as possible after surgery; a common feature of the negative trials is their late start of therapy. Whether the pathophysiologically desirable administration of the antiplatelet agent even before surgery is feasible, remains to be shown.

The necessary duration of a prophylactic antiplatelet therapy after aortocoronary bypass surgery has not been investigated; since the spontaneous bypass occlusion rate seems to be very low after the first year (approximately 2.5% annually (Campeau *et al.*, 1977)), a therapy seems unwarranted for the late period. The study by Chesebro *et al.* (1982) was unable to identify any subgroups not profiting from therapy; a favourable effect was found independent of bypass blood flow, lumen diameter of the anastomosed coronary artery or coronary artery anastomosed.

In the light of the current evidence and of our experience, we recommend prophylactic administration of 100 mg ASA daily in the absence of contraindications to all patients after aortocoronary bypass surgery, starting as early as 6–10 h post-operatively and continuing for one year. In our opinion, this recommendation is justified in spite of the small size of our trial, since it is supported by pathophysiological insights and positive trends in similar trials.

Our trial confirms the efficacy of low-dose ASA (100 mg once daily) as an antiplatelet agent and warrants further clinical trials of this regimen for related indications in arterial disease.

This work was supported in part by the Deutsche Forschungsgemeinschaft.

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(Received September 29, 1983, accepted February 3, 1984)

Appendix

To correct for the unequal number of anastomoses at base-line, subordinate 2 × 2 contingency tables were constructed for each number of anastomoses and then combined using the method of Woolf (Miller, 1980). He proposed that the logarithms of the approximate relative risk (i.e. the cross-product ratio) from different tables can be combined by weighting them inversely proportional to their variance. If a_i, b_i, c_i, d_i are the numbers in the cells, then:

$$CP_i = a_i \, d_i \cdot b_i \, c_i$$

where CP_i: cross-product in the ith subordinate table

$$\text{In CPcom} = (\Sigma \, (\text{In } CP_i \times 1/Var_i))/\Sigma \, 1/Var_i$$

where CPcom is the combined cross-product and Var_i = Variance $(\ln CP_i) = 1/a_i + 1/b_i + 1/c_i + 1/d_i$ and the approximate variance thereof:
Var (ln CPcom) = $1/\Sigma \, (1/\text{Var } (\ln CP_i))$.