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The Influence of the Amalgam Alloy on the Survival of Amalgam Restorations: A Secondary Analysis of Multiple Controlled Clinical Trials

H. Letzel, M.A. Van 't Hof¹, G.W. Marshall², and S.J. Marshall²

Dental School, University of Nijmegen, Postbus 9101, 6500 HB Nijmegen, The Netherlands; present address, Groesbeekseweg 223, 6523 NV Nijmegen, The Netherlands; ¹Department of Medical Statistics, University of Nijmegen; ²Department of Restorative Dentistry, Box 0758, University of California, San Francisco, San Francisco, California 94143-0758, USA; *to whom correspondence and reprint requests should be addressed

Abstract. Data from 14 independent controlled clinical trials on the oral behavior of Classes 1 and 2 amalgam restorations, with a follow-up between five and 15 years, were re-evaluated by secondary analysis for the influence of alloy composition on the survival of amalgam restorations. For the analysis, 3119 restorations were available, which were made from 24 different alloys by a group of seven operators. The alloys were divided into four groups according to their zinc content (zinc-containing and zinc-free) and their copper content (conventional and high-copper). During the follow-up of the trials, the restorations were annually assessed for failures, which were classified as to (1) restoration-, (2) restorative process-, and (3) patient-related reasons. With the restoration-related failures, survival functions of the restorations were estimated by alloy and alloy group. The total number of failed restorations was 481, of which 77% were restoration-related and 14% process-related. Eighty percent of the restoration-related failures were due to some form of fracture of the amalgam. Restorations of conventional zinc-free alloys had the shortest survival. After 13 years, only 25% survived. Zinc and a high copper content had an equally favorable influence on the survival rate, which was 70% after 13 years when either was present. The highest survival rates were of restorations of zinc-containing high-copper alloys: 85% after 13 years. Zinc and copper contents of the alloy contributed to the corrosion resistance of the amalgams, which in turn influenced the survival of the restoration. The current ISO Standard 1559 on alloys for dental amalgam should be modified to account for these factors that influence the survival of amalgam restorations.

Key words: amalgam alloy, restoration survival, clinical trials, secondary analysis, corrosion.

Introduction

Many different amalgam alloys have been introduced since the appearance of dental amalgam more than 150 years ago. At present, most of the alloys on the market in the Western industrialized world satisfy the requirements of Standard 1559: Alloys for Dental Amalgam [International Organization for Standardization (ISO), 1986]. The ISO standard can be traced back almost a century, when the effects of the chemical composition of an alloy on its physical properties (dimensional change, strength, and flow of amalgam) were extensively investigated (Black, 1908). For producers, the standard offers guidelines for the production and marketing of alloys. For clinicians, the standard is of less interest because the clinical significance of the requirements is limited.

From a clinical point of view, the quality of an amalgam alloy can be expressed in the life span or survival of restorations made from it. The first attempts at analysis by survival were done in retrospective studies (Robinson, 1971; Allan, 1977; Crabb, 1981). The progressive failure of the four groups of restorations in the three studies has been transformed into survival rates (or proportional cumulative survival) in Fig. 1. The median lifetimes of the groups were from six to 11 years. For the determination of cause-effect relationships with respect to survival, however, retrospective studies cannot be used, because of their observational nature.

Influences on the survival of dental restorations can be investigated with long-term controlled clinical trials. In a clinical trial on three alloys, Osborne et al. (1980a) showed that after eight years the amalgam alloy had a significant influence on the survival rate of amalgam restorations due to bulk fracture. Similar studies have been done with different alloys and follow-up times, but with the same results (Doglia et al., 1986; Letzel et al., 1989; Van Dijken, 1991). The results of the four studies are summarized in Table 1. In general, restorations of high-copper alloys have a
higher survival rate than those of conventional alloys. This is commonly attributed to the higher corrosion resistance of high-copper amalgams, due to the absence of the corrosion-prone gamma two phase in amalgam. However, there are exceptions to this rule (Alloys NT and AG, Table 1). Based on this result, it was postulated that when the corrosion resistance of the alloy has a causal relation with the survival of the restoration, the zinc content of the alloy has an influence on the survival, because zinc is the least corrosion-resistant component in the alloy (Marshall et al., 1987; Sarkar and Park, 1988).

At the University of Nijmegen Dental School, 14 independent long-term controlled clinical trials have been conducted on influences on the survival of posterior amalgam and composite restorations. The results of the trials, however, are limited, because each trial had its own objectives, had a limited number of restorations at baseline, and in general suffered from long-term patient drop-out, so that the power for the detection of survival influences was weak. These limitations can be overcome if the survival data of the independent trials are pooled and analyzed simultaneously on survival influences.

Pooling of original data from various studies was first proposed 25 years ago (Light and Smith, 1971) and was further developed in educational research in the 1970s. General purposes of pooling data are: (1) to improve the estimate of an effect, i.e., to increase the power of the effect, to resolve uncertainty when studies disagree; and (2) to answer questions that were not or could not have been posed at the start of the studies. Two methods of pooling can be distinguished: meta-analysis and secondary analysis (Glass, 1976). In a meta-analysis, a group of previous studies with common underlying characteristics is critically reviewed, and the primary results of each study are analyzed statistically, so that the results can be integrated. Meta-analysis is a relatively new technique and has been done on the results of controlled clinical trials of resin-bonded bridges (Creugers and Van 't Hof, 1991) and posterior composite restorations (El-Mowafy et al., 1994). In a secondary analysis, the original data of a group of trials are first merged into one file, so that one large "observational study" is obtained. Next, influences of variables are re-analyzed directly. The advantage of such a re-analysis is that direct estimations of effects of variables are more precise, i.e., have a smaller standard error. The disadvantage of such a re-analysis is that results can be erroneous due to confounding of variables, which in turn is caused by the loss of randomization of the variables, when the trials are merged into one file. Secondary analysis has not previously been applied to clinical trials on dental restorations.

In this paper, a re-evaluation is described of the influence of the copper and zinc content of the amalgam alloy on the survival of amalgam restorations using pooled survival data of the 14 University of Nijmegen Dental School controlled clinical trials. The re-evaluation also is preceded by a comparison of the precision of alloy effect estimations on the survival obtained with the two abovementioned data-pooling methods. The re-evaluation also is preceded by an investigation into the potential confounding of the amalgam alloy with other experimental variables, when the trials were re-evaluated by secondary analysis. The objective of the preceding analyses was to choose the most suitable method for the re-evaluation of the survival data.

### Materials and methods

#### The clinical trials

In the period 1974-1983, 14 trials on the oral behavior of Classes I and II amalgam and composite restorations were initiated. Each trial had its own specific objectives, experimental design, and protocol. The main characteristics of the trials are listed in Table 2. Details of a number of trials have been described in previous publications on influences on the short-term clinical

![Figure 1. Cumulative survival rates of four groups of amalgam restorations. The curves are transformations of the original progressive failure data as published by the authors.](image-url)

### Table 1. Published survival rates in percentages of amalgam restorations by alloy

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up Time (yrs)</th>
<th>Total No. Restorations</th>
<th>AA</th>
<th>MC</th>
<th>PR</th>
<th>SF</th>
<th>NT</th>
<th>CA</th>
<th>SH</th>
<th>AG</th>
<th>DI</th>
<th>SY</th>
<th>TI</th>
<th>LU</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osborne et al.</td>
<td>8</td>
<td>105</td>
<td>76</td>
<td>65</td>
<td>83</td>
<td>72</td>
<td>94</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td>89</td>
<td>100</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Doglia et al.</td>
<td>5</td>
<td>103</td>
<td>83</td>
<td></td>
<td>76</td>
<td>89</td>
<td>88</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letzel et al.</td>
<td>5</td>
<td>387</td>
<td></td>
<td>83</td>
<td>76</td>
<td>89</td>
<td>88</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letzel et al.</td>
<td>7</td>
<td>295</td>
<td></td>
<td>83</td>
<td>76</td>
<td>89</td>
<td>88</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Dijk et al.</td>
<td>6</td>
<td>126</td>
<td></td>
<td>83</td>
<td>76</td>
<td>89</td>
<td>88</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* AA = Aristalloy, Englehard Industries, USA; MC = Twentieth Century Micro Cut, Caulk, USA; PR = Premix, Cendres et Metaux, Switzerland; and EP = Epoque 80, Scania Dental, Sweden. For other alloy names, see corresponding codes in Table 4.*

Patients for the trials were mainly selected from university students, staff, and their relatives. Selection criteria were: an acceptable level of oral hygiene, complete or almost complete dentition, the need for a sufficient number of Classes I and II restorations, and availability for long-term follow-up. The total number of patients was 615; their mean age at the placement of the restorations was 25 years (Table 2). Slightly more males (60%) than females entered the trials. Each patient was treated by only one operator. Depending on the design of the trial, the number of restorations per patient ranged from one to 12.

The restorations were placed by a group of seven operators with characteristics listed in Table 3. The group was heterogeneous with respect to age and professional experience. Within each trial, the selected patients were assigned at random to the participating operators. The experimental variables were the restorative material and three factors in the restorative process (Table 2). Twenty-four amalgam alloys were included in the trials, several of them in more than one trial, and there was a wide variety in type and composition. Within each trial, a single batch of each amalgam alloy was used. When the same alloy was used in more than one trial, the batch number was sometimes the same and sometimes different. The restorative process factor in four trials was: (1) condensation method (Trials 2 and 5: hand vs. mechanical amalgam condensation techniques), (2) isolation method (Trial 3: rubber dam vs. cotton rolls), and (3) polishing (Trial 6: burn-ish only vs. burnish + polish). Within each trial, the levels of the experimental variables were assigned at random to the teeth selected for restoration. Details of the variables can be obtained from the references listed in Table 2. In total, 3244 experimental amalgam restorations were made.

The 24 amalgam alloys used in the trials were divided into four groups according to their copper and zinc content, as indicated by + and - subscripts. The groups were:

- (1) conventional zinc-free alloys (Cu, Zn)
- (2) conventional zinc-containing alloys (Cu, Zn)
- (3) high-copper zinc-free alloys (Cu, Zn)
- (4) high-copper zinc-containing alloys (Cu, Zn)

Conventional alloys had a copper content of 6% (Cu) and high-copper alloys 12% or more (Cu). Alloys which contained 0.3% or more zinc were classified as zinc-containing (Zn). The trade names and manufacturers of the alloys are listed in groups in Table 4. Six alloys were experimental and not commercially available. Figs. 2a and 2c show representative restorations directly after placement made of a Cu, Zn alloy (SH) and a Cu, Zn alloy (DI), respectively.

Conventional cavities of all types and sizes were prepared according to "extension for prevention" principles. All materials were prepared according to the manufacturers' directions for use, and the restorations were placed under isolation with rubber dam. Cavities for amalgam were lined with calcium hydroxide when they were deep, based on operator judgment. Amalgams were

<table>
<thead>
<tr>
<th>Trial No.</th>
<th>Baseline Year</th>
<th>No.</th>
<th>Patients' Mean Age</th>
<th>% Female</th>
<th>Retrieval Rate in 1988/89</th>
<th>No. of Restorations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1974</td>
<td>57</td>
<td>23</td>
<td>57</td>
<td>55</td>
<td>360</td>
</tr>
<tr>
<td>2</td>
<td>1976</td>
<td>106</td>
<td>23</td>
<td>23</td>
<td>15</td>
<td>719</td>
</tr>
<tr>
<td>3</td>
<td>1977</td>
<td>76</td>
<td>23</td>
<td>35</td>
<td>36</td>
<td>484</td>
</tr>
<tr>
<td>4</td>
<td>1977</td>
<td>78</td>
<td>24</td>
<td>56</td>
<td>60</td>
<td>546</td>
</tr>
<tr>
<td>5</td>
<td>1978</td>
<td>49</td>
<td>26</td>
<td>52</td>
<td>61</td>
<td>250</td>
</tr>
<tr>
<td>6</td>
<td>1978</td>
<td>48</td>
<td>26</td>
<td>42</td>
<td>60</td>
<td>300</td>
</tr>
<tr>
<td>7</td>
<td>1979</td>
<td>14</td>
<td>24</td>
<td>52</td>
<td>64</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>1982</td>
<td>17</td>
<td>26</td>
<td>41</td>
<td>88</td>
<td>132</td>
</tr>
<tr>
<td>9</td>
<td>1983</td>
<td>25</td>
<td>26</td>
<td>30</td>
<td>88</td>
<td>125</td>
</tr>
<tr>
<td>10</td>
<td>1983</td>
<td>48</td>
<td>24</td>
<td>32</td>
<td>65</td>
<td>162</td>
</tr>
<tr>
<td>11</td>
<td>1980</td>
<td>48</td>
<td>24</td>
<td>32</td>
<td>65</td>
<td>228</td>
</tr>
<tr>
<td>12</td>
<td>1982</td>
<td>18</td>
<td>26</td>
<td>29</td>
<td>67</td>
<td>123</td>
</tr>
<tr>
<td>13</td>
<td>1983</td>
<td>23</td>
<td>25</td>
<td>28</td>
<td>74</td>
<td>54</td>
</tr>
<tr>
<td>14</td>
<td>1983</td>
<td>31</td>
<td>25</td>
<td>56</td>
<td>87</td>
<td>102</td>
</tr>
</tbody>
</table>

Total (Mean) 615b (25) (40) (54) 3639 (3244 amalgams)

Table 2. Characteristics of the trials

Table 3. Operators' Characteristics

- SD between 4 and 7.
- Several patients participated in more than one trial.
- Trials 11, 12, and 14 were designed to evaluate the oral behavior of composite restorations, and amalgam served as a positive control. Trial 13 contained no such amalgam control group and is included only for a complete view of the 14 trials.
- CM = Condensation Method, IM = Isolation Method, and PM = Polishing Method.
- Two variations of the same alloy.
- Most operators participated in more than one trial (see Table 3).
- Some materials were used in more than one trial.
condensed and burnished by hand, and all polished restorations were polished after a minimum of 24 hrs following placement. In the four trials in which a restoration process factor was an experimental variable, one level of the factor was the standard procedure as described above (Trials 2, 3, 5, and 6, Table 2).

**Survival analysis**

After placement of the restorations, the patients were re-called at least once a year for re-examination. The last re-call was in 1988-1989, so that the follow-up time for the restorations was between five and 15 years. The re-call rate of the patients at the last re-call for each trial and the mean rate over all trials are given in Table 2. It can be seen that the shorter the follow-up time, the higher the re-call rate. In Trials 2 and 3, the relatively low re-call rates (15 and 36%, respectively) were due to the large number of dental students participating as patients in those trials. After graduation, many of these patients did not come back for re-examinations. In general, the reasons for patient drop-out were “moving without leaving a new address” and “time limitations because of a new and busy occupation”.

Table 3. Operator characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Birth Year of Graduation</th>
<th>Sex</th>
<th>Employment (%)</th>
<th>Participation in Trials</th>
<th>Number of Restorations Placed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1927</td>
<td>Male</td>
<td>School 20 80</td>
<td>1,2,3,4,5,8,11,13,14</td>
<td>1105</td>
</tr>
<tr>
<td>2</td>
<td>1938</td>
<td>Male</td>
<td>80 20</td>
<td>1,2</td>
<td>419</td>
</tr>
<tr>
<td>3</td>
<td>1935</td>
<td>Male</td>
<td>80 20</td>
<td>2,3,4,6,7,9,11,14</td>
<td>1070</td>
</tr>
<tr>
<td>4</td>
<td>1951</td>
<td>Male</td>
<td>50 50</td>
<td>3,4,6</td>
<td>496</td>
</tr>
<tr>
<td>5</td>
<td>1935</td>
<td>Male</td>
<td>80 20</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>6</td>
<td>1940</td>
<td>Male</td>
<td>20 80</td>
<td>10,11,14</td>
<td>260</td>
</tr>
<tr>
<td>7</td>
<td>1943</td>
<td>Female</td>
<td>100 -</td>
<td>12,13</td>
<td>164</td>
</tr>
</tbody>
</table>

Reasons such as lack of interest or discontent with the treatment or the annual re-examination procedure were infrequent, so that selective patient dropout probably did not occur.

At the annual re-calls, the restorations were carefully examined for failures by one of the operators, who acted as evaluator. It was not possible to assign re-call patients at random to the evaluators, so that, in a number of cases, restorations were evaluated by the operator who made them.

The reason why a restoration failed was carefully ascertained. In this context, a restoration was defined as having failed when the tooth containing the restoration was missing, when a replacement was unavoidable to prevent further damage to the tooth, or when the patient wanted the restoration replaced for esthetic reasons. Restorations with a clinically unacceptable extent of marginal deterioration—that is, Category 6 of the Nijmegen Photo Rating Scale for marginal deterioration (Marshall et al., 1987)—were also considered to be failures for the purpose of this analysis.

For the survival analysis, the date at which a restoration was first classified as failed was taken as the failure date of the restoration. This was usually an annual re-call date. In a few cases, patients made appointments on their own initiative when they noticed that something had happened to a restoration. When such a restoration had to be replaced, the appointment date was taken as the failure date. The dates at which restorations classified as not failed were seen for the last time were used to calculate (randomly censored) survival times. Restorations of patients who dropped out were considered as lost to follow-up. Using the censored survival times, we estimated survival functions of groups of restorations according to the methods of Kaplan and Meier (1958). In Fig. 3, survival functions are...
Figure 2. (a) Restoration of a Cu,Zn alloy (Shofu Spherical) after placement and (b) after six years with an unacceptable extent of marginal fracture. (c) Restoration of a Cu,Zn alloy (Dispersalloy) after placement and (d) after six years with negligible marginal fracture.

depicted graphically as survival curves, including standard errors. The curves are drawn as long as possible in time in such a way that the standard error never exceeds 10%. Effects of experimental variables were tested for their significance with the Proportional Hazard Model (Cox, 1972).

To trace the causes of failure, we classified all failure reasons according to a system which distinguishes among three types of failures (Letzel et al., 1989):

Type 1: Failure directly related to the restoration (i.e., the material and the way it was manipulated).

Type 2: Failure related to the restorative process (i.e., the results of the decision-making process of the operator).

Type 3: Failure related to external factors (i.e., caused by extra-oral influences, which are related neither to the restoration nor to the restorative process).

Influences investigated for association with survival in this study were:

(1) The operator (7 levels).
(2) The material (24 amalgam alloys = 24 levels).
(3) The process for amalgam restorations (3 factors, each with 2 levels).

To evaluate the influence of the operator, we assumed that Type 3 failures were not caused by the operator. Therefore, only
Figure 3. Survival functions (Kaplan and Meier, 1958) of amalgam restorations made by five operators (Nos. 1-5) of alloys with medium survival quality. The lowest curve is Operator 5 and the second lowest Operator 2. Vertical lines represent standard errors.

Types 1 and 2 failures were taken into account in the survival analysis. Restorations with Type 3 failures were considered lost to follow-up. The same assumption was made when the influence of the restorative process was analyzed. When the influence of the restorative material was analyzed, it was assumed that Types 2 and 3 failures had no causal relation to the material, so that, for this analysis, only Type 1 failures were used. Types 2 and 3 failures were then considered restorations lost to follow-up.

We investigated the precision of alloy effect estimations by comparing the sizes of the standard errors derived from meta-analysis and secondary analysis on the 10-year survival rate of two alloys used in different trials. The potential confounding of the amalgam alloy effect with that of the operator and the restorative process factor effects was investigated by provisional secondary analyses of the effects of the three variables.

Results

Meta-analysis vs. secondary analysis

The comparison of the sizes of the standard error of the alloy effect on the 10-year survival rate obtained by meta-

analysis and secondary analysis is summarized in Table 5. In the Table, the survival rate is listed for three alloys used in two different trials. Alloy DI (Dispersalloy) was used in both trials, while alloys LU (Luxalloy) and IN (Indiloy) were used in different trials. With a meta-analysis, the standard error of the estimated difference between the 10-year survival rates of alloys IN and LU was 9.0%. When the same difference was estimated with a secondary analysis, the standard error was smaller (6.9%).

The provisional secondary analysis showed that some factors of the restorative process have a minor influence on the survival of the restorations. On the other hand, the amalgam alloy and the operator both have a strong survival influence. The magnitude of these two variables is given in Table 6. In the Table, the lowest and highest 10-year survival rates of amalgam alloy and operator are listed, including the standard errors (SE). The rates show that both variables were strongly heterogeneous, which is an indication that the two variables are confounded.

For further provisional secondary analysis, survival functions of the restorations of the four alloy groups (Table 4) were estimated. The results showed that, with respect to survival, the alloy groups could be divided into three clusters, which are:

Cluster 1: low survival (alloy group Cu2Zn).
Cluster 2: medium survival (alloy group Cu2Zn and CuZn).
Cluster 3: high survival (alloy group CuZn).

An estimation of survival functions of the operator within each cluster revealed that the operator effect was significant only in Cluster 2. Survival curves of the restorations made by the five operators in this cluster are depicted in Fig. 3. The operator effect was mainly caused by Operator 5, who participated in only one trial and produced 125 restorations of one medium survival alloy in 25 patients (Tables 2 and 3). After 10 years, only 50% of his restorations had survived. When the restorations of Operator 5 were deleted, and only restorations of medium survival alloys were considered, the initially detected significance of the influence of the restorative process factors disappeared. To overcome confounding problems, we decided to exclude the restorations of Operator 5 for further analysis. After this exclusion, confounding was no longer regarded as a serious problem. This and the results of the comparison of the standard errors as summarized in Table 5 led us to choose

Table 5. The standard error (SE*) of the effects of two alloys (IN and LU), each used in a different trial, on the 10-year survival rate of amalgam restorations

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Trial</th>
<th>Amalgam Alloy</th>
<th>10-Year Survival Rate (%)</th>
<th>SE</th>
<th>Effect (%)</th>
<th>SE</th>
<th>Effect (%)</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-</td>
<td>2</td>
<td>DI (Dispersalloy)</td>
<td>91.9</td>
<td>4.5</td>
<td>DL2 - LU2 = 22.6</td>
<td>7.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>LU (Luxalloy)</td>
<td>69.3</td>
<td>5.6</td>
<td>DL4 - IN4 = 4.5</td>
<td>5.4</td>
<td>(DL2 - LU2) - (DL4 - IN4) = 18.1</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>IN (Indiloy)</td>
<td>88.7</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>2</td>
<td>LU (Luxalloy)</td>
<td>69.3</td>
<td>5.6</td>
<td></td>
<td></td>
<td>IN4 - LU2 = 19.4</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>IN (Indiloy)</td>
<td>88.7</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* SE obtained with a meta-analysis and a secondary analysis.
Figure 4. Survival curves of amalgam restorations made of (a) Cu-Zn alloys, (b) Cu-Zn alloys, (c) Cu-Zn alloys, and (d) Cu-Zn alloys. For alloy names, see the corresponding codes in Table 4. Vertical lines represent standard errors. Note: The survival functions of alloy El within the Cu-Zn group and of the consolidated group within the Cu(Zn) group are not depicted, because they are covered by other functions.

secondary analysis as the most suitable way of survival data analysis. The number of amalgam restorations available for this analysis thus was 3244 - 125 = 3119.

Failures
Of the 3119 amalgam restorations at baseline, 481 had failed by the end of the follow-up. Divided into Types 1, 2, and 3 failures, the numbers (and percentages) were 371 (77%), 66 (14%), and 44 (9%), respectively. The numbers of Types 1, 2, and 3 failures by reason for failure are listed in Table 7. Within Type 1 failures, six reasons can be distinguished, and within Types 2 and 3 failures, four reasons were noted. For an impression of the age of the failed restorations, the follow-up was divided into three time periods. Type 1 (restoration-related) failures due to bulk and marginal ridge fracture manifested themselves throughout the follow-up. The development of marginal fracture and discoloration, however, took more than four years to reach an unacceptable level. The majority of Type 1 failures were fractures of the amalgam (Bulk and Marginal Ridge Fracture + Severe Marginal Fracture = 48 + 32 = 80%), although the timing of the fractures was quite different. Only 5% of the Type 1 failures were due to recurrent caries.

With respect to Type 2 (process-related) failures, restorations were considered to have failed for tooth fracture, when an enamel cusp was partially or totally fractured. The majority of Type 2 failures were tooth fracture (32 = 48%).

Pulpal involvement was interpreted as a Type 2 failure reason, when a root canal treatment was necessary, for which the restoration had to be removed. Most of those treatments were necessary within five years after placement.

The reasons for failure of the 44 Type 3 failures (caused by external influences) included 35 cases of primary caries located on a proximal surface of the tooth that was caries-free at the time of placement (80%). In addition, there were five tooth and/or restoration fractures due to traffic, sport, and
Survival

The survival curves of restorations of the alloys within the four alloy groups (according to Type 1 failures) are shown in Fig. 4. Five alloys in the Cu+Zn group and six alloys in the Cu+Zn+ group had 27 or fewer restorations at baseline (Table 4). Since these numbers were too small for meaningful survival estimations, the restorations of these alloys within the two groups were consolidated into groups (n = 126 and 150, respectively; see Table 4), and from these two consolidated groups, survival functions were estimated. Survival curves of restorations of the two alloys of the Cu-Zn group are depicted in Fig. 4a. In the long term, the curves are not significantly different. The median lifetime of the restorations is approximately ten years. A characteristic clinical example of this type is pictured in Fig. 2b. The survival curves of restorations of the Cu+Zn+ alloy group are shown in Fig. 4b. The alloy type within this group has no significant influence on the survival, which starts to decrease at about six years. Fig. 4c contains the survival curves of restorations of the Cu+Zn+ alloy group. The group is slightly heterogeneous, which is caused exclusively by the high survival of alloy AR. Generally, the survival of the alloys also begins to decrease at six years. The survival curves of restorations of the two alloys and of the consolidated group of the Cu+Zn+ alloy group are shown in Fig. 4d. The alloy group is homogeneous, and there is only a slow and gradual decrease in the survival. A representative clinical picture of a restoration of these alloys is given in Fig. 2d.

To illustrate the general influence of the copper and zinc content of the alloy on the survival, we put the alloys within the four groups together and estimated the survival function for each group. The number of restorations at baseline and the follow-up time of each group can be derived from the numbers listed in Table 4. The survival curves of the four groups are depicted in Fig. 5. It can easily be seen that the alloy composition has a strong influence on the survival. The survival rate of the Cu-Zn group is the lowest. At 13 years, this was 25%. The Cu+Zn and the Cu+Zn+ groups have the same survival, 70% at 13 years. The longest survivals are in the Cu+Zn+ alloy group. At 13 years, 85% of the restorations had survived.

Discussion

Originally, the trials were designed to investigate influences on the short-term clinical behavior of characteristics of restorations, such as marginal fracture of amalgam restorations. However, during the follow-up of the trials, it became clear that the prospective value of such characteristics for the survival of the restorations is questionable, and that an investigation of survival effects on the restorations would be much more relevant for clinical dentistry. Therefore, it was decided to extend the clinical behavior to survival studies. Since the number of short-term failures of the restorations within each trial was rather small, it was decided to follow the restorations as long as possible and to re-analyze the trials simultaneously after the end of the follow-up by combining survival data. As such, with this re-analysis, questions were answered that were not and could not have been posed at the start of the trials (Glass, 1976).

The results of the comparison of the sizes of the standard errors showed that a direct survival effect estimation with secondary analysis is more precise than an indirect estimation with meta-analysis. This conclusion can be generalized, because direct comparisons always have lesser uncertainty than indirect comparisons. Confounding of influences of variables is the major potential drawback to secondary analysis. For these analyses, confounding has
been eliminated in two distinct ways:

(1) stratification of the alloy variable into three homogeneous subgroups with respect to their survival; and
(2) exclusion of data which disturb further analyses.

(This was done for one operator who made a limited number of restorations of one alloy.)

In this secondary analysis, the restorations were considered as independent units. However, the average number of restorations per patient was six, which means that the restorations were not fully independent of each other, and that the patient also can have an influence on the survival of his restorations. However, due to the selection procedure for patients for the trials, the patient group was homogeneous with respect to dental health awareness. Therefore, the patient influence on the survival of the restorations was minor and should not result in erroneous cause-effect relationships or in different standard errors in the Kaplan-Meier curves.

When the survival data are re-analyzed in the ways described above for a secondary analysis, the major confounding influences are eliminated. However, there are other influences which may act as confounders, such as the restoration class, the width of the restoration (Osborne and Gale, 1990), the patient sample included in the trials, and the duration of the participation of the operators. For the moment, it is assumed that these potential confounders will not seriously affect estimates. Although confounding can never be eliminated completely, when the major confounding influences are neutralized, survival effects can be estimated by a secondary analysis to an acceptable level of accuracy. Therefore, this pooling method led to the best survival effect estimates and was deemed the most suitable approach for a simultaneous re-analysis of the trials in this study.

When the clinical behavior of the amalgam restorations in the trials was carefully followed for about 13 years, most restorations failed for reasons directly related to the restoration (Table 7). Of those, at least 80% were due to some form of fracture of the amalgam, which means that the amalgam was not strong enough to withstand forces of mastication over an extended period of time. The number of cases with recurrent caries and unacceptable discoloration was very small, so these phenomena were not leading reasons for failure. Process-related failures originated in misjudgments of the operator during the selection of teeth for restoration, the design and preparation of the cavity, and/or the preparation made before the application of amalgam. Tooth fracture and pulpal involvement could have been avoided if the operator had not selected the tooth for restoration, because the cavity was too large and/or too deep. Unacceptable proximal contact and cervical adaptation were the result of faulty matrix application and wedging. Process-related failures can be limited to an acceptable level by correct operative procedures but can never be avoided completely, even when the operator has extensive clinical experience.

The incidence of primary caries was not representative of the general patient population, because the patients in the trials comprised an incidental sample, which was narrowly selective. Patients were accepted for participation in the trials based on their dental interests and relatively high level of oral hygiene at the time of entrance into the studies, as well as the need for at least six restorations.

The reasons for replacement of amalgam restorations have been analyzed many times in retrospective studies, resulting in an age distribution or an average age of replaced restorations (Mjör, 1981). Although such studies are quick to perform and often quoted, the results may not be compared with those of survival studies, because replacement studies do not give information about survival. The comparison of the two types of studies has led to much confusion in discussions on the survival of amalgam restorations (Osborne and Norman, 1990).

In general, the survival of a dental restoration is influenced by three factors: (1) the restoration material, (2) the process performed by the operator, and (3) external influences induced by the patient. The system used in this analysis to classify the reasons for failure into three types...
offers an opportunity for investigation of the influence of the composition of the amalgam alloy separately from those of the other two causative factors. The system also can be used for survival studies of other filling materials.

The most surprising result of the secondary analysis was that the composition of the alloy had a tremendous influence on the life span of amalgam restorations. Those of conventional zinc-free alloys have by far the shortest survival. Shortly after placement, they started to fail, resulting in a 13-year survival of 25%, when only the restoration-related failure reasons are taken into account. It is common knowledge that the gamma two phase in conventional alloys rapidly corrodes in the oral environment (Wagner, 1962; Jørgensen, 1965). This results in a reduction of the strength of the amalgam, so that the restoration becomes vulnerable to fracture when subjected to masticatory forces. Therefore, corrosion is the underlying cause of the short survival of restorations of conventional alloys. An early clinical manifestation of corrosion is marginal fracture. This phenomenon was first described 30 years ago (Jørgensen, 1965), and this rapid form of deterioration of restorations of conventional zinc-free alloys has been found many times since then in short-term clinical trials (Letzel and Vrijhoef, 1984b).

The favorable influence of a high copper content of the alloy on its survival is not surprising and, in fact, was expected. This improvement has been demonstrated frequently in clinical trials (Osborne and Norman, 1990): Restorations of high-copper alloys have less marginal fracture than those of conventional alloys (Mahler et al., 1970). However, the improvement has a temporary effect on survival, because after about six years, the survival rate starts to decline. Apparently, the corrosion is diminished and not stopped. Nevertheless, the median survival time cannot be estimated, since the 13-year survival is 70%.

A small amount of zinc in the alloy has an important favorable effect of the same magnitude as that of high-copper content. With respect to corrosion, its influence is paradoxical. On the one hand, zinc is the least noble and most electro-active component in amalgam and dissolves very quickly (Johansson and Dérand, 1983). On the other hand, it seems to reduce overall corrosion. The paradox can be explained by the sacrificial function of zinc in amalgam. It corrodes first and thereby delays the corrosion of the gamma two phase (Sarkar and Park, 1988). The favorable influence of zinc on the corrosion of conventional amalgam restorations has also been found in clinical studies (Wilson and Ryge, 1963; Watson et al., 1973): Restorations of zinc-containing alloys have less marginal fracture than those of zinc-free alloys. The corrosion reduction of zinc has the same temporary effect on survival as does high-copper content. After about six years, the survival rate starts to decline. Again, the median survival time cannot be estimated, because the 13-year survival rate is 70%.

Restorations of high-copper alloys, which also contain a small amount of zinc, have the longest survival. Apparently, zinc reduces the corrosion not only of conventional amalgams, but also of high-copper amalgams. Again, this was found in a clinical trial (Berry et al., 1986): After two years, restorations of zinc-containing high-copper alloys have less marginal fracture than those of their zinc-free counterparts. The sacrificial behavior of zinc delays the corrosion of the Cu-Sn phase in the amalgam. An indication of this behavior was found in a microstructural investigation of retrieved pieces of failed restorations of zinc-containing high-copper alloys (Marshall et al., 1987). The restoration surface in contact with the cavity wall frequently consisted of a thick layer of zinc-containing corrosion products, which presumably was formed by a first and selective corrosion attack of the zinc-containing phase in the amalgam. This finding also suggests that the zinc stays trapped at the interface. Remarkably, pieces of failed restorations of this alloy were very difficult to remove with hand instruments and seemed to adhere strongly to the cavity wall. This can be explained by phosphorus and calcium, which also were found in the zinc-containing layer and which may have created some form of adhesion of the amalgam to the cavity wall. It is not known whether a high zinc concentration at the tooth-amalgam interface has additional biological effects on the clinical behavior of amalgam restorations. It may have bactericidal properties and thus can have a preventive effect on the formation of recurrent caries. In any case, the biological consequences of zinc accumulation at the tooth-amalgam interface need to be investigated further.

The survival of restorations of zinc-containing high-copper alloys decreases slowly with time, resulting in a 13-year survival rate of 85%. Restorations of these alloys have the highest resistance to corrosion.

During preliminary stages of the survival analysis, many methods were attempted to divide the alloys into homogeneous groups with respect to their survival behavior. Dividing the alloys into four groups according to a specific minimum copper and zinc content was found to be best. Only alloy AR did not fit the system. While it is a zinc-free, high-copper alloy, it behaves like a zinc-containing, high-copper alloy, which means that AR has a high corrosion resistance. A clinical illustration of this resistance is shown in Fig. 5 (AR restorations 13 years after placement). The exceptional behavior of the alloy may be explained by its high silver (80%) and low tin content (7%) (Bengel, 1990). This exception is an indication that metals other than copper and zinc may also have an influence on the corrosion of amalgam and survival of amalgam restorations.

It appears that the chemical composition of the alloy determines its corrosion resistance, which, in turn, determines the survival of the restoration. Based on the results of this secondary analysis, two elements of the alloy have been identified which appear to increase the survival of the restoration and act by inhibiting corrosion. The first composition factor is a copper content of 12% or more, and the second, a zinc content of 0.3% or more; these appear to act synergistically. The influence of alloy composition on survival must be investigated more thoroughly. This can be done with other secondary analyses of long-term controlled clinical trials on amalgam restorations in which other alloys with different compositions are involved. This may lead to the identification of other protective elements.

When the quality of an alloy is expressed in the survival of restorations, the results of this study indicate that three quality levels can be distinguished: low, medium, and high.
Low-quality alloys had neither composition factor, and restorations made with them had limited lifetimes. Medium-quality alloys contained one factor and are suitable for making relatively durable restorations. High-quality alloys contained both factors, and restorations of them are capable of long-term survival (85% after 13 years). The influence of the alloy composition on the survival of restorations is long-term and requires a follow-up time of at least ten years. Results of studies with a shorter follow-up, such as those summarized in Table 1, are therefore only suggestive.

The survival of restorations made for clinical trials cannot be strictly compared with that of restorations evaluated in observational studies in private practices and institutional settings (Robinson, 1971; Allan, 1977; Crabb, 1981). Yet the survival rates in Fig. 1 somewhat resemble the survival curves of restorations of conventional zinc-free alloys as shown in Fig. 4a. This resemblance can be explained by the alloy used and the operator characteristics in the observational studies. The restorations were placed in the 1950s and 1960s and therefore can have been made of only conventional alloys. The zinc-free version of those alloys was probably used, because such alloys were the most popular at that time. Furthermore, a general practitioner who investigates the fate of amalgam restorations which he made 10 to 20 years previously and publishes the results of his investigation is probably highly skilled. Similarly, operators who participate in clinical trials on amalgam restorations probably have the same skill levels, which further enhances the similarity between the curves in Figs. 1 and 4a. The slight difference may be attributed to differences between the methods used to analyze survival. Only restoration-related failures were used to investigate the survival influence on alloy composition in this study, while in the observational studies, all failures were used.

The results of the secondary analysis show that the current Standard 1559 for dental amalgam alloys (International Standardization Organization, 1986) is not predictive of amalgam survival, because all four alloy groups satisfy the composition requirement and because there is no requirement for corrosion resistance. The relevance of the standard can be improved by reformulation of some of the composition requirements. Among others, the minimum copper content should be changed from 6 to 12%, and the alloy should contain zinc, unless the producer can show that, with his alloy, equivalent performance can be expected. The warning that zinc in the alloy can cause delayed expansion of an amalgam thus contaminated should be modified or deleted. This warning is a relic from the past, and delayed expansion can generally be prevented in modern "four-handed" dentistry. Moreover, contaminated zinc-containing high-copper amalgam does not expand as much as contaminated zinc-containing conventional amalgam (Osborne and Berry, 1992). The standard should also contain a requirement for minimum corrosion resistance and a method to test this resistance. The design of such a test, however, will be difficult, because the clinical corrosion process is very complicated (Marshall et al., 1992).

The validity of marginal fracture as a criterion in clinical behavior studies of amalgam restorations has always been questionable. On the basis of a clinical and laboratory test of three alloys, a relation was suggested between marginal fracture after one year and the rheologic properties dynamic creep, static creep, and slow compressive strength (Mahler et al., 1970). The results of this study, and of many similar correlation studies, probably led to the ISO standard for creep. However, it has been shown that there is no correlation between marginal fracture after 2 to 2.5 years and creep when more alloys are involved in the correlation study (Osborne et al., 1980b; Vrijhoef and Letzel, 1986). This means that the significance of short-term marginal fracture is not clear, and neither is creep. This study and the reinterpretation of other marginal fracture studies which are mentioned in this paper suggest that short-term marginal fracture formation has a certain prognostic value for the survival of the restoration. This needs to be investigated further and may lead to a re-appraisal of the significance of marginal fracture.

The existence of a long-term correlation between marginal fracture and survival offers an opportunity for the design of a short-term clinical test for amalgam alloys, which has more relevance for clinical dentistry than Standard 1559 (International Standardization Organization, 1986). Such a test can be designed to conform to the draft of Standard 10993 (International Standardization Organization, 1991). According to the definitions of this draft, an amalgam alloy is a dental device, as are all other dental filling materials. The adoption of this standard will result in the acceptance of only effective alloys, that is, alloys providing restorations with demonstrable long-term survival. This, in turn, should result in an improvement of the benefit-to-cost ratio of restorative dental care with amalgam.

The availability of only effective amalgam alloys should also help reduce mercury pollution of the environment. Longer-lasting amalgam restorations are replaced less often and thus will decrease future discharges of amalgam waste into sewage systems. This discharge is rapidly becoming a political issue, at least in Western Europe (European Economic Community, 1984).

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