Saving Lives by Modifying the Process of Science: Estimated Historical Mortality Associated with the Failure to Conduct Routine Prospective Cumulative Systematic Reviews

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Abstract
Cumulative meta-analysis, or “living systematic reviews,” can save lives. Using epidemiologic methods and findings from a classic study of interventions to reduce heart attack mortality (Antman 1992), we estimated annual deaths that may have occurred because cumulative meta-analyses were not conducted. Failure to use knowledge that would have been available with cumulative meta-analysis may have resulted in 41,000 deaths annually from non-use of intravenous dilators, 35,000 deaths annually from aspirin non-use, and 37,000 deaths annually from β-blockers non-use. The consequences of failure to routinely conduct cumulative meta-analyses are 1) non-use of effective interventions, 2) continued use of ineffective/harmful interventions, and 3) unnecessary research.

Background
In 1992, Antman and colleagues published a pioneering study demonstrating that knowledge of the effectiveness, ineffectiveness, or harm associated with 15 interventions to reduce mortality among patients who had suffered acute myocardial infarctions (MIs) could have improved medical practice [1]. Effective interventions could have been adopted, but were not; ineffective and harmful interventions could have been discontinued. Effective medical practices were delayed for years甚至 decades because ongoing systematic reviews of the state of knowledge were not conducted as new research emerged. The methodology of “living systematic reviews” (LSR) has recently been developed for the conduct of cumulative meta-analyses. To demonstrate the benefits of this approach, we use data from the Antman study to estimate the mortality likely to have resulted from the failure to use LSR [2].

Methods
We estimate mortality associated with four interventions analyzed by Antman: three interventions that reduce mortality-intravenous vasodilators administered during hospitalization, and β-blockers and aspirin administered during and after hospitalization, and one intervention that increases mortality-Class 1 anti-arrhythmic drugs [1,3]. Antman’s study reports the year in which cumulative meta-analysis first indicated benefit (or harm) for each intervention, and the year in which the intervention became routine in practice (or was eliminated because it was found to be ineffective or harmful) [1]. Routine practice was assessed by examination of reviews and texts focused on the intervention published each year. Published reviews and texts were classified as recommending use routinely, recommending use in...
specific circumstances, recommending use rarely or never, or as experimental or not mentioned.

We used information from available studies about mortality from acute MI during and after hospitalization to estimate mortality attributable to failure to use (or use of) each intervention assessed. While the numbers of deaths associated with MI have changed over the study period, we use the number of deaths at the approximate Antman study period midpoint, i.e., 1980, to estimate attributable mortality. We use the method of population attributable risk (PAR) to estimate the number of deaths that might have been averted [4].

\[ PAR = P_e \frac{(RR-1)}{((P_e(RR-1)) + 1)}, \]

where \( P_e \) is the prevalence of practice nonuse, and RR is the relative risk of death associated with nonuse of the practice. With 100% nonuse, the equation becomes \( PAR = \frac{RR-1}{RR} \). In sensitivity analyses, we assess the benefits of partial adoption, i.e., \( P_e < 100\% \), or changing other parameters. We estimate RR as the inverse of the odds ratio.

We also assessed research that may have been unnecessary had cumulative meta-analysis been used and the delay in adoption of demonstrably effective interventions by practitioners [4]. From Antman’s analysis, we report the number of RCTs that followed finding of effectiveness, the number of patients in these trials, and the delay between the year of cumulative meta-analysis finding and evidence of practice. Because conditions surrounding MI in the U.S. have changed since the publication of Antman’s study, we conducted a sensitivity analysis for one of the interventions reviewed—the use of aspirin. We varied the prevalence of use of the interventions assessed, included all (rather than only first) MIs within ICD code 410, and considered the possibility that effect sizes were half of what was found by Antman.

**Mortality associated with MI**

We used an estimate of the number of MI patients in the population with an acute MI (ICD code 410) in 1980. We use fatality rates for first and subsequent MIs from a synthesis of estimates of associated pre-hospital, in-hospital, and post-hospital mortality rates to reconstruct the number of first and subsequent MIs in 1980, in-hospital deaths, and deaths within 3 years post-discharge [5,6] (Table 1). We assume that the reporting of ICD 410 is for first MI and reconstruct subsequent MIs using proportions from other sources. (https://www.cdc.gov/heartdisease/facts.htm) In a sensitivity analysis, we assume ICD 410 includes first and subsequent MIs. Approximately 225,000 MI patients died before reaching the hospital, i.e., 49% of deaths (Table 1). There were an estimated 95,000 in-hospital deaths (15.2% of patients admitted to the hospital) and 137,000 (25.9% of patients discharged from the hospital) post-hospital deaths in 1980 (Table 1).

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated MIs in US</th>
<th>pre hospital death (9% incidence)</th>
<th>pre hospital death</th>
<th>Hospital admission</th>
<th>Hospital case fatality</th>
<th>In-Hospital deaths</th>
<th>MI patients discharged alive</th>
<th>Mortality year 1st year</th>
<th>Mortality after first year</th>
<th>Deaths post discharge —3 years</th>
<th>Deaths post hospital 3 yrs</th>
<th>Total deaths acute MI, 1980</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First acute MI, 1980</strong></td>
<td>559,740</td>
<td>0.23</td>
<td>126,740</td>
<td>431,000</td>
<td>0.13</td>
<td>56,030</td>
<td>374,970</td>
<td>0.10</td>
<td>0.05</td>
<td>74,594</td>
<td>131,024</td>
<td></td>
</tr>
<tr>
<td><strong>Subsequent acute MI, 1990</strong></td>
<td>260,222</td>
<td>0.33</td>
<td>65,772</td>
<td>194,449</td>
<td>0.2</td>
<td>38,860</td>
<td>165,559</td>
<td>0.2</td>
<td>0.1</td>
<td>62,224</td>
<td>101,113</td>
<td></td>
</tr>
<tr>
<td><strong>Total acute MI, 1990</strong></td>
<td>819,962</td>
<td>0.22</td>
<td>192,514</td>
<td>625,449</td>
<td>0.2</td>
<td>94,890</td>
<td>530,520</td>
<td>0.2</td>
<td>0.1</td>
<td>137,218</td>
<td>232,137</td>
<td></td>
</tr>
</tbody>
</table>

**Results and Discussion**

**Estimating mortality attributable to intervention nonuse/use**

In the hospital setting, the annual number of deaths associated with the non-use of interventions that would have been available had cumulative meta-analyses been conducted range from 12,000 for the non-use of intravenous or oral \( \beta \)-blockers to 41,000 for the non-use of intravenous vasodilators (Table 2).

In the post-hospital setting, the annual number of deaths attributable to failure to use secondary preventive measures that could have been available are 14,000 for the non-use of anti-platelet drugs (predominantly aspirin) and 26,000 for the non-use of oral \( \beta \)-blockers (Table 2). The use of type I antiarrhythmic drugs was found to be harmful, with a summary odds ratio of 1.28 (Table 2). Their routine use is estimated to be associated with 39,000 deaths annually (Table 2).
Table 2: Annual Deaths Attributable to Non-Use of Interventions for Acute MI in A. Acute Treatment, and B. 3 Years Post-Discharge.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>yr meta anal finding</th>
<th>yr routine use</th>
<th>gap years</th>
<th>final OR</th>
<th>RRI death with intervention nonuse</th>
<th>PAR %</th>
<th>Increased deaths/yr with intervention nonuse in Hospital Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. MORTALITY IN ACUTE MI IN HOSPITAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intravenous vasodilators (nitrroglycerin and nitropusside)</td>
<td>1981 (&lt;0.05)</td>
<td>1990</td>
<td>9</td>
<td>0.57 (0.41 - 0.79)</td>
<td>1.75</td>
<td>0.43</td>
<td>40,686</td>
</tr>
<tr>
<td>aspirin</td>
<td>1988 (&lt;0.00001)</td>
<td>1990</td>
<td>2</td>
<td>0.77 (0.70 - 0.84)</td>
<td>1.3</td>
<td>0.23</td>
<td>21,905</td>
</tr>
<tr>
<td>intravenous or oral β-blockers</td>
<td>1986 (&lt;0.05)</td>
<td>1991</td>
<td>5</td>
<td>0.80 (0.69 - 0.98)</td>
<td>1.14</td>
<td>0.12</td>
<td>11,657</td>
</tr>
<tr>
<td>B. MORTALITY FOLLOWING ACUTE MI (SECONDARY PREVENTION) AFTER HOSPITAL DISCHARGE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antiplatelet drugs/ASPIRIN</td>
<td>1981 (&lt;0.05)</td>
<td></td>
<td></td>
<td>0.90 (0.82 - 1.00)</td>
<td>1.11</td>
<td>0.10</td>
<td>13,585</td>
</tr>
<tr>
<td>oral β-blockers,</td>
<td>1977 (&lt;0.05)</td>
<td>1983</td>
<td>6</td>
<td>0.81 (0.73 - 0.89)</td>
<td>1.23</td>
<td>0.19</td>
<td>25,456</td>
</tr>
<tr>
<td>type I antiarrhythmic drugs</td>
<td>1981 (&lt;0.05)</td>
<td></td>
<td></td>
<td>1.28 (1.22 - 1.31)</td>
<td>0.78</td>
<td>-0.28</td>
<td>-38,703</td>
</tr>
</tbody>
</table>
The data sources for the present analysis are less than optimal and our analysis rests on unverifiable assumptions. Feinlieb noted in 1984, "Unfortunately, this country has no method or system for standardized complete reporting of new MIs and no incidence data representative of the national population"—a situation that has not changed [7]. Estimates of the incidence of MIs range between 450,000 and 600,000, indicating that our estimate is consistent with other reports. In addition, data are not available on interventions actually used or on patient adherence to treatments, particularly after discharge [7,8]. Moreover, there are likely interactions among interventions that might affect outcomes. Nevertheless, while the estimation of mortality in this analysis required many simplifying assumptions, the number of deaths from failure to use existing information and apply it is unarguably large.

The circumstances of MI have changed greatly since the period examined here. The incidence of MIs has declined, due partly to the interventions reviewed by Antman and because of changes in population behavior, e.g., smoking [9]. Our purpose here is not to portray the current state of MIs, but to use historical data to indicate how the standard practice of science may severely hinder effective knowledge and practice and lead to unnecessary harm and unneeded research [10,11]. The process of building knowledge and applying it in medicine and public health needs fundamental revision. Ongoing cumulative meta-analysis should be routine but requires a process of prioritization and systematic methods. The development of living systematic reviews establishes an essential foundation for this project [2,11].

**References**