sess its effect on major adverse cardiac events.[1] Rates of any cardiac hospitalization were 5% in the intervention group vs 16% in the usual care group. The approximately 70% relative risk reduction and 11% absolute risk reduction in hospitalization for major adverse cardiac events or heart failure are much higher than would be expected for even the most potent intervention or treatment in this setting. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, for example, 3086 almost exclusively statin-naïve patients were randomized to receive high-dose atorvastatin (80 mg/d) or placebo.[8] Even one of the most impressive treatments in our therapeutic armamentarium, which, in the MIRACL study, lowered low-density lipoprotein cholesterol level by 40%, led to far more modest risk reductions in cardiac events requiring hospitalization than the reductions reported for enhanced depression care in the COPES trial. Indeed, most of the effect of high-dose statin treatment in the MIRACL study was due to a 26% relative risk reduction and 2% absolute risk reduction in hospitalization for myocardial ischemia. Thus, while the results of the COPES trial are provocative and exciting, they must be replicated in larger, appropriately powered trials before the promising reduction in hospitalizations can be used to calculate potential cost savings.

Ladapo et al[2] should be congratulated for addressing the economic impact of their findings and for conducting a randomized controlled trial in patients with ACS, a difficult enough task in and of itself. However, the task before medical professionals when interpreting studies like this is also challenging. Coping with rising health care costs requires us to carefully examine all the resources that would be involved in implementing "more health care" and then, equally, to carefully determine whether this would actually lead to "better health" by evaluating the net gain to patients and society. Whether the COPES trial is good value for the money remains unclear.

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## RESEARCH LETTERS

### Stability of Active Ingredients in Long-Expired Prescription Medications

Debate exists regarding the relative potency of medications beyond their labeled expiration dates. Expired medications have not necessarily lost potency, since the expiration date is only an assurance that the labeled potency will last at least until that time.[1] Clinical situations may arise in which expired drugs might be considered owing to lack of viable alternatives[2] or financial concerns.[3] Ongoing studies show that many medications retain their potency years after their initially labeled expiration dates.[4] We sought to characterize the potency of some prescription medications that had expired decades ago.

**Methods.** Eight long-expired medications with 15 different active ingredients were discovered in a retail pharmacy in their original, unopened containers. All had expired 28 to 40 years prior to analysis. Three tablets or capsules of each medication were analyzed, with each sample tested 3 times for each labeled active ingredient. No analytical standard for homatropine could be found, so that ingredient was not tested.

Tablets or capsule contents were dissolved and sonicated in methanol, reconstituted in analysis buffer (10% methanol) and analyzed with Liquid Chromatograph (Agilent Technologies) Time-of-Flight Mass Spectrometer (Agilent) using electrospray ionization in negative and positive polarities. Chromatography was run with gradient elution using Eclipse Plus C18 column (Agilent). Data analysis was performed using Mass Hunter Qualitative and Quantitative Analysis (Agilent). Quantification was performed by isotope dilution method with a 6-point calibration curve.

**Table. Declared and Measured Amounts in Drugs**

| Drug Trade Name With Active Ingredients | Declared Amount, mg | Measured Amount, Mean (SD), mg |
|---|---|---|
| Somnafac | | |
| Methaqualone | 200.0 | 240.3 (20.6) |
| Fiorinal with codeine No. 1 | | |
| Codeine | 7.5 | 7.4 (0.3) |
| Butalbital | 50.0 | 51.1 (1.6) |
| Aspirin | 200.0 | 2.28 (0.10) |
| Phenacetin | 130.0 | 142.8 (7.1) |
| Caffeine | 40.0 | 51.2 (4.8) |
| Codempiral No. 3 | | |
| Codeine | 32.4 | 29.3 (2.6) |
| Phenobarbital | 16.2 | 15.2 (0.2) |
| Aspirin | 226.8 | 1.53 (0.04) |
| Phenacetin | 162.0 | 87.8 (2.7) |
| Bamadex | | |
| Meprobamate | 300.0 | 390.8 (44.9) |
| Amphetamine | 15.0 | 8.1 (0.9) |
| Obocell | | |
| Amphetamine | 5.0 | 2.2 (0.1) |
| Nebralin | | |
| Pentobarbital | 90.0 | 105.1 (7.4) |
| Seconal | | |
| Secobarbital | 100.0 | 90.5 (7.1) |
| Hycomine | | |
| Hydrocodone | 5.0 | 5.2 (0.4) |
| Homatropine | 1.5 | Not tested |
| Chlorpheniramine | 2.0 | 6.1 (0.2) |
| Acetaminophen | 250.0 | 249.2 (38.3) |
| Caffeine | 30.0 | 30.3 (1.8) |

**Results.** Twelve of the 14 drug compounds tested (86%) were present in concentrations at least 90% of the labeled amounts, the generally recognized minimum acceptable potency. Three of these compounds were present at greater than 110% of the labeled content. Two compounds (aspirin and amphetamine) were present in amounts of less than 90% of labeled content. One compound (phenacetin) was present at greater than 90% of labeled amounts from 1 medication tested, but less than 90% in another medication that contained that drug (**Table**).

**Comment.** The US Food and Drug Administration (FDA) permits "reasonable variation," such that most medications marketed in the United States contain 90% to 110% of the amount of the active ingredient claimed on the label.[5] Drug expiration dates typically range from 12 to 60 months after their production.[4] However, FDA regulations do not require determination of how long medications remain potent after that, allowing manufacturers to arbitrarily establish expiration dates without determining actual long-term drug stability.

The Shelf-Life Extension Program (SLEP) checks long-term stability of federal drug stockpiles. Eighty-eight percent of 122 different drugs stored under ideal environmental conditions had their expiration dates extended more than 1 year, with an average extension of 66 months and a maximum extension of 278 months.[4] In our data set, 12 of 14 medications retained full potency for at least 336 months, and 8 of these for at least 480 months. Given our inability to confirm ideal storage conditions for our samples, our results support the effectiveness of broadly extending expiration dates for many drugs, the efficacy of which has been demonstrated by SLEP in a more controlled fashion.

The 3 drugs found with less than 90% of their labeled potency were amphetamine and aspirin in both samples tested and phenacetin in 1 of 2 samples tested. Aspirin is known to degrade in vitro,[6] but there are no such published data regarding amphetamine. For phenacetin, the difference in recovery between the 2 samples could be due to differences in packaging or storage of the containers. Aside from aspirin, all drugs in Fiorinal (butalbital, aspirin, caffeine, and codeine phosphate) had almost 100% of labeled concentrations, while those of Codempiral No. 3 (phenacetin with codeine phosphate) were all less than 95%. Since the codeine measured in Codempiral No. 3 was also lower than that of Fiorinal (90% vs 99%), this suggests that Codempiral's packaging was less intact, allowing moisture to penetrate, which can promote hydrolysis. Because phenacetin has an amide functional group, it is more prone to this type of degradation than codeine.

Three drugs were unexpectedly found in our samples at potencies greater than 110% of the labeled amounts. Some samples may have been produced prior to 1963, when FDA-mandated quality control measures were instituted (Paula R. Katz, Regulatory Counsel, FDA, Center for Drug Evaluation and Research, Division of Manufacturing and Product Quality, Guidance and Policy; e-mail communication, May 23, 2011); however, exact dating of all our samples was not possible. Alternately, these drugs could have come from lots untested by the manufacturer, or the accuracy between analytical methods used in this study compared with those used decades ago could be questioned.

The most important implication of our study involves the potential cost savings resulting from lengthier product expiration dating. Each dollar spent on SLEP to demonstrate longer than labeled drug stability results in $13 to $94 saved on reacquisition costs.[4] Given that Americans currently spend more than $300 billion annually on prescription medications,[7] extending drug expiration dates could yield enormous health care expenditure savings.

In conclusion, this study provides additional evidence that many prescription pharmaceuticals retain their full potency for decades beyond their manufacturer-ascribed expiration dates. Given the potential cost-savings, we suggest the current practices of drug expiration dating be reconsidered.

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## Persistence With Therapy Among Patients Treated With Warfarin for Atrial Fibrillation

The major challenges of warfarin therapy relate to poor adherence and persistence, the need for regular monitoring, and the risk of hemorrhage. In clinical trials, persistence with warfarin treatment ranges from 75% to 79% at 1 year,[1,2] but persistence in clinical practice is thought to be poorer. Small observational studies suggest that approximately one-quarter of patients cease warfarin treatment within a year of initiation.[3,4] To our knowledge, there are currently no large studies offering real-world estimates of persistence among warfarin users.

*See Invited Commentary at end of letter*

The objective of this study was to examine persistence with warfarin therapy in a large population-based cohort of newly treated patients with atrial fibrillation (AF).

**Methods.** We conducted a population-based cohort study among residents of Ontario, Canada, 66 years and older, who commenced treatment with warfarin between April 1, 1997, and March 31, 2008. We used multiple linked administrative data sets from Ontario, the most populous province in Canada, to identify outpatient prescription records, hospitalizations, emergency department visits, physician services, patient demographics, and comorbidities. Details of these databases are given in the eAppendix (http://www.archinternmed.com). The data were held securely in a linked, deidentified form and analyzed at the Institute for Clinical Evaluative Sciences.

For each study subject, we identified a period of continuous warfarin use beginning with the first prescription dispensed after their 66th birthday and defined by successive prescription refills within 180 days, thereby allowing for periodic dose adjustments, brief lapses in adherence, and variable timing of prescription refills. To create an inception cohort of patients with AF, patients with any prescription for warfarin in the preceding year were excluded, and the analysis was restricted to patients who had a physician visit, emergency department assessment, or hospital admission for AF or flutter in the 100 days preceding the first prescription for warfarin. We followed patients from their cohort entry date until the first instance of discontinuation of warfarin therapy, death, or the end of the study period (March 31, 2010), with a maximum follow-up of 5 years.

We constructed Kaplan-Meier curves to characterize drug therapy discontinuation. Secondary analyses described persistence with warfarin therapy according to age (66 to 75 years, 76 to 85 years, and ≥86 years), sex, $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score,[5] and date of warfarin therapy initiation (before or after April 1, 2003; presuming progressive improvements in anticoagulation management over time).[6,7] The log-rank test was used to examine differences in persistence among patient subgroups. This research was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

**Results.** Over the 13-year study period, we identified 125 195 new users of warfarin in Ontario 66 years or older with a recent diagnosis of AF. Of these, 86 432 (69.0%) had a $CHADS_2$ score of 2 or higher at the outset of therapy, and 62 851 (50.2%) initiated treatment within a week of their AF diagnosis.

Of 125 195 patients who started warfarin therapy for AF, 8.9% did not fill a second warfarin prescription during follow-up, 31.8% discontinued therapy within 1 year, 43.2% discontinued therapy within 2 years, and 61.3% discontinued therapy within 5 years (**Figure**). The median time to discontinuation (MTD) was 2.9 years. Men discontinued warfarin therapy earlier than women (MTD, 2.6 years vs 3.2 years, respectively; $P<.001$), while patients aged 66 to 75 years were more likely to discontinue therapy compared with older patient groups (MTD, 2.7 years vs 3.1 years for patients >85 years; $P<.001$). Persistence with warfarin therapy increased with stroke risk, as reflected by the $CHADS_2$ score (MTD, 2.3 years, 2.9 years, and 3.3 years among people with a $CHADS_2$