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Effect of Angiotensin Converting Enzyme Inhibition on Sudden Cardiac Death in Patients Following Acute Myocardial Infarction

A Meta-Analysis of Randomized Clinical Trials

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OBJECTIVES Estimate the effect of angiotensin converting enzyme (ACE) inhibitors on the risk of sudden cardiac death (SCD) following myocardial infarction (MI).

BACKGROUND Trials in post-MI patients have shown that ACE inhibitor therapy reduces mortality. However, the effect on SCD as a mechanism has not been clarified.

METHODS Trials of ACE inhibitor therapy following MI reported between January, 1978 and August, 1997 were identified. Studies were included if they met the following criteria: 1) randomized comparison of ACE inhibitor to placebo within 14 days of MI; 2) study duration/blinded follow-up of ≥6 weeks; 3) the number of deaths and modes of death were reported or could be obtained from the investigators.

RESULTS We identified 374 candidate articles, of which 15 met the inclusion criteria. The 15 trials included 15,104 patients, 2,356 of whom died. Most (87%) fatalities were cardiovascular and 900 were SCDs. A significant reduction in SCD risk or a trend towards this was observed in all of the larger ($N > 500$) trials. Overall, ACE inhibitor therapy resulted in significant reductions in risk of death (random effects odds ratio [OR] = 0.83; 95% confidence interval [CI] 0.71–0.97), cardiovascular death (OR = 0.82; 95% CI 0.69–0.97) and SCD (OR = 0.80; 95% CI 0.70–0.92).

CONCLUSIONS This analysis is consistent with prior reports showing that ACE inhibitors decrease the risk of death following a recent MI by reducing cardiovascular mortality. Moreover, this analysis suggests that a reduction in SCD risk with ACE inhibitors is an important component of this survival benefit. (J Am Coll Cardiol 1999;33:598–604) © 1999 by the American College of Cardiology

Following an acute myocardial infarction, patients are at significantly increased risk of cardiovascular death and nonfatal reinfarction (1). Reduced left ventricular function and dilatation that result from the infarction and the subsequent ventricular remodeling process are important components of this enhanced risk (2–4). Sudden cardiac death (SCD) accounts for about half of the deaths in these patients (1). The propensity to fatal arrhythmias is increased by structural changes and the degree of left ventricular dysfunction. Neurohumoral activation, which occurs following acute myocardial infarction, may also be arrhythmogenic and contribute to the risk of SCD.

Large, randomized clinical trials have shown that angiotensin converting enzyme (ACE) inhibitors improve survival in postmyocardial infarction patients (5–10). A number of the actions of the ACE inhibitors are likely to be important in this mortality reduction. These agents attenuate left ventricular dilatation and thereby result in less ventricular enlargement (11). Further, two large studies with long term follow-up, the Survival and Left Ventricular Enlargement (SAVE) Trial (5) and the Studies of Left Ventricular Dysfunction (SOLVD) (12), have demonstrated a reduction in the risk of subsequent myocardial infarction in patients treated with ACE inhibitors. Since the majority of patients who die suddenly have fresh coronary thrombus, the reduction in risk of myocardial infarction may be important in reducing the risk of SCD. Also, the ACE inhibitors have been shown to be sympatholytic (13) and to preserve plasma potassium, which reduces the like-

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AAD = antiarrhythmic drug
CI = confidence interval
MI = myocardial infarction
OR = odds ratio
SCD = sudden cardiac death

lihood of malignant ventricular arrhythmias. These beneficial effects of ACE inhibition are believed to be helpful in preventing SCD. Since SCD is only a component of cardiovascular mortality, no single trial could be adequately powered to address the mechanistic question of the therapeutic effect of ACE inhibitor therapy on this mode of death.

METHODS

Data identification. We attempted to identify all randomized trials of ACE inhibitors in patients following acute myocardial infarction published between January, 1978 and August, 1997. We searched for studies in the MEDLINE database (National Library of Medicine). Study abstracts were reviewed and those that could not be excluded, based on criteria listed below, were reviewed in full. Reference lists of these papers and of relevant review articles were scrutinized for sources of additional published data.

Studies were included if they met the following criteria: 1) randomized comparison of an ACE inhibitor to placebo in patients with a history of myocardial infarction within the prior 14 days, 2) study duration ≥6 weeks and blinded follow-up for ≥6 weeks and 3) total mortality, cardiovascular mortality and SCD mortality were reported or could be obtained from the investigators. These criteria were chosen to reduce the influence of deaths during the periinfarction period in order to study the effect of ACE inhibitor on SCD unrelated to the index infarction and to reduce the potential for bias associated with not using a placebo control.

Definitions of sudden cardiac death. Deaths were classified as "sudden cardiac" from information in the published manuscripts (11 trials) or by contacting the authors (four trials). Specifically, five of the 15 trials utilized an endpoints committee to validate "sudden deaths" using a prespecified definition of unexpected death within one hour of symptom onset (5–7,14–16). These 5 trials contributed 867 of the 900 (96%) sudden deaths. A prespecified definition of sudden death was used in this paper to label the causes of death in seven other trials. The definition utilized was "sudden unexpected collapse without documentation of arrhythmia or collapse due to intractable ventricular tachycardia/fibrillation." Deaths were classified using information available in the published manuscript in three trials (17–19) and by obtaining this information directly from the authors in four additional trials (20–23). These seven trials contributed 20 (2.2%) additional sudden cardiac deaths. In two trials, deaths were labelled as sudden cardiac without further description (24–25). These two trials contributed 13 (1.5%) deaths. In the remaining trial no deaths were reported (26).

Statistical methods. Separate analyses were performed for SCD, all cardiac deaths and total mortality. Observations were pooled using a weighted average, with weights inversely proportional to the variance of the effects. To calculate the odds ratios a constant of 0.5 was added to all counts to improve the estimation of the odds ratios and their variances (27). The summary odds ratios for the three analyses were calculated both for the DerSimonian and Laird random effects methods and for the Mantel-Hanszel fixed effects methods (28). The random effects method was chosen, a priori, for the primary analysis. Cochran's test was used to examine the homogeneity of the treatment effects across trials overall with respect to each endpoint and among the subsets of trials with follow-up of <6 months duration and those with ≥6 months duration (28). Since three trials had a follow up of exactly 6 months, the subgroups with ≤6 months duration and >6 months duration were also considered. A sensitivity analysis was performed in which each trial was deleted in turn and the metaanalysis recomputed. The purpose of this analysis was to make certain that the overall results did not depend solely on a single, influential trial. Individual and overall random effects odds ratios (OR) with corresponding 95% confidence intervals (CI) are reported. Furthermore, logistic regression was used to evaluate the influence of the baseline characteristics of the individual trials (Table 1) on the observed effect of ACE inhibitors on SCD, and simple linear regression was used to assess the relationship of trial duration and the effect of ACE inhibitors on SCD. These analyses were performed using SAS 6.10 and Stata Release 5.0 statistical packages.

RESULTS

Pooling of trials. We identified 374 articles whose abstracts were retrieved and carefully reviewed for possible inclusion. Abstracts were examined and studies eliminated if they did not meet the inclusion criteria. Thirty studies that remained candidates for inclusion after examination of their abstracts were retrieved in full. Of these studies, eight were excluded because the active therapy or follow-up period was less than 6 weeks (8,10,29–34), one due to initiation of therapy more than 14 days after myocardial infarction (35), one because not all of the patients had suffered a myocardial infarction (36), one because it was a preliminary report of data subsequently reported and included in the present analysis (37), and four due to the absence of a placebo control group (9,38–40). The remaining 15 trials used in this analysis (5–7,14–25) included a total of 15,104 patients (7,658 randomized to active therapy and 7,446 to placebo).

Table 1. Baseline Characteristics

Study (by duration)	Year	Drug	Follow-up	Age	Male	EF	β-blocker	CCB	Aspirin	HTN	DM	Lytic
(45–179 days)												
Mortarino[26]	1990	captopril	2 months	57	76%	0.36	0%	0%	0%	—	—	—
Oldroyd[24]	1991	captopril	2 months	60	83%	0.36	—	—	—	25%	7%	0%
Nabel[17]	1991	captopril	3 months	54	82%	0.50	34%	29%	—	—	—	100%
Sharpe[25]	1991	captopril	3 months	58	83%	0.41	21%	19%	—	32%	—	72%
SMILE[14]	1995	zofenopril	6 weeks	64	73%	—	20%	10%	54%	40%	21%	0%
EDI[20]	1997	enalapril	6 weeks	62	87%	0.33	49%	—	96%	31%	—	69%
ECCE[18]	1997	enalapril	3 months	62	80%	0.46	52%	13%	54%	16%	10%	63%
(≥180 days)												
CONSENSUS 2[15]	1992	enalapril	6 months	66	73%	—	67%	23%	—	—	11%	56%
SAVE 2[15]	1992	captopril	42 months	59	83%	0.31	36%	42%	59%	43%	22%	33%
AIRE[7]	1993	ramipril	15 months	65	74%	—	22%	16%	78%	28%	12%	58%
PRACTICAL[19]	1994	enalapril/captopril	12 months	64	73%	0.45	17%	17%	—	—	—	72%
Søgaard[21]	1994	captopril	6 months	59	91%	0.40	76%	—	100%	17%	12%	81%
CATS[22]	1994	captopril	12 months	60	75%	0.54	13%	0%	32%	22%	9%	100%
TRACE[6]	1995	trandolapril	24–42 months	67	72%	≤ 0.35	16%	28%	91%	23%	14%	45%
EDEN[23]	1997	enalapril	6 months	56	91%	0.48	28%	6%	84%	—	—	59%

CCB = calcium channel blocker; DM = diabetes mellitus; EF = mean ejection fraction; HTN = hypertension; Lytic = thrombolytic therapy at the time of myocardial infarction.

Baseline characteristics of the patients in each of the 15 trials are shown in Table 1.

Mortality results (Table 2 and Fig. 1). There were 2,356 deaths, of which 302 (13%) were noncardiovascular and 2,054 (87%) were cardiovascular. Of the 2,054 cardiovascular deaths, 900 (44% of cardiovascular deaths and 38% of total deaths) were considered to be sudden by the investigators. Of the 7,658 ACE inhibitor assigned patients, there were 1,105 (14.4%) deaths, and of the 7,446 patients in the placebo group, there were 1,251 (16.8%) deaths (OR = 0.83; 95% CI 0.71–0.97). Cardiovascular death occurred in 958 (12.5%) of active treatment patients and 1,096 (14.7%) of placebo treated patients (OR = 0.82; 95% CI 0.69–0.97). SCD occurred in 407 (5.3%) ACE inhibitor treated patients and 493 (6.6%) of placebo patients (OR = 0.80; 95% CI 0.70–0.92). In contrast, noncardiovascular death occurred in 147 (1.9%) of treated and 155 (2.1%) of placebo patients (OR = 0.87; 95% CI 0.69–1.09).

Impact of trial duration and baseline covariates. Study duration was not correlated with the observed odds ratios for SCD (Fig. 1). This was evidenced by the homogeneity of the results in both trials <6 months and those ≥6 months in duration ($p > 0.79$). While trials <6 months in duration were homogeneous for cardiovascular and total mortality ($p > 0.30$), trials ≥6 months were not homogeneous for these endpoints ($p < 0.01$). Furthermore, trials ≤6 months and >6 months in duration were homogeneous with respect to all three endpoints ($p > 0.41$). Finally, study duration was not significantly linearly correlated with the odds ratio for SCD in each trial ($p = 0.60$).

A logistic regression model with dichotomous variables for each trial and treatment group yielded a similar highly significant effect of ACE inhibitors on reducing SCD (OR = 0.80; 95% CI 0.70–0.92; $p \leq 0.001$). While the use of aspirin, beta-adrenergic blocking agents, calcium channel blockers and thrombolytic therapy varied among the trials, as did the prevalence of diabetes and hypertension (Table 1), these variables were not significant when added to the logistic regression model ($p > 0.28$) and had only a small effect on the estimated treatment effect.

Sensitivity analyses. We did not include the GISSI-3 trial (9) in the primary analysis because it was not placebo-controlled and lisinopril was only prescribed for 42 days. However, we were able to obtain the number of SCD, cardiac deaths and total deaths during the initial 42 days (personal communication: Aldo Maggioni). When the GISSI-3 results were considered along with the 15 trials included in the primary analysis, a similar protective effect of ACE inhibitors was observed on SCD (OR = 0.81; 95% CI 0.72–0.89; $p < 0.001$).

The ISIS-4 trial also was not included in the primary analysis since information on the mode of death was not collected and the trial duration was only 35 days (8). However, a similar impact on overall mortality was observed (OR = 0.88; 95% CI 0.80–0.96; $p = 0.005$) when the results of ISIS-4 were considered along with the original set of trials and GISSI-3.

A further sensitivity analysis removed each of the 15 trials in turn and recomputed the odds ratios. Very similar point estimates resulted. In particular, the results were unchanged even with the omission of CONSENSUS 2, the largest trial. Overall, the trials were homogeneous with respect to SCD ($p = 0.90$) but not with respect to cardiovascular mortality ($p = 0.05$). For mortality, lack of homogeneity

Table 2. Baseline Characteristics

	Sample Size		Total Mortality			Cardiovascular Mortality			Sudden Cardiac Death		
	ACE	Placebo	ACE	Placebo	OR (95% CI)	ACE	Placebo	OR (95% CI)	ACE	Placebo	OR (95% CI)
Mortarino[26]	10	11	0	0	1.10 (0.02–60.30)	0	0	1.10 (0.02–60.30)	0	0	1.10 (0.02–60.30)
Oldroyd[24]	49	50	8	5	1.69 (0.54–5.36)	8	5	1.69 (0.54–5.36)	4	4	1.02 (0.26–4.02)
Nabel[17]	20	18	0	1	0.29 (0.01–7.44)	0	1	0.29 (0.01–7.44)	0	1	0.29 (0.27–7.44)
Sharpe[25]	50	50	3	2	1.43 (0.27–7.61)	3	2	1.43 (0.27–7.61)	3	2	1.43 (0.27–7.61)
SMILE[14]	772	784	50	65	0.77 (0.52–1.12)	48	63	0.76 (0.52–1.12)	4	11	0.39 (0.13–1.18)
EDI[20]	47	42	1	0	2.74 (0.11–69.15)	1	0	2.74 (0.11–69.15)	0	0	0.90 (0.02–46.09)
ECCE[18]	104	104	2	3	0.71 (0.14–3.67)	2	3	0.71 (0.14–3.67)	1	0	3.03 (0.12–75.22)
CONSENSUS 2[15]	3044	3046	312	286	1.10 (0.93–1.31)	299	270	1.12 (0.94–1.33)	86	88	0.98 (0.72–1.32)
SAVE[5]	1115	1116	228	275	0.79 (0.64–0.96)	188	234	0.77 (0.62–0.95)	105	125	0.83 (0.63–1.08)
AIRE[7,16]	1004	982	170	222	0.70 (0.56–0.87)	161	207	0.72 (0.57–0.90)	89	121	0.69 (0.52–0.93)
PRACTICAL[19]	150	75	12	12	0.46 (0.20–1.06)	9	12	0.34 (0.14–0.83)	5	4	0.60 (0.17–2.16)
Søgaard[21]	29	29	1	1	1.00 (0.10–10.20)	1	1	1.00 (0.10–10.20)	1	0	3.11 (0.12–79.43)
CATS[22]	149	149	13	10	1.31 (0.57–3.05)	11	10	1.10 (0.46–2.63)	3	4	0.77 (0.19–3.18)
TRACE[6]	876	873	304	369	0.73 (0.60–0.88)	226	288	0.71 (0.58–0.87)	105	133	0.76 (0.58–1.00)
EDEN[23]	239	117	1	0	1.48 (0.06–36.56)	1	0	1.48 (0.06–36.56)	1	0	1.48 (0.06–36.56)
Overall	7658	7446	1105	1251	0.83 (0.71–0.97)	958	1096	0.82 (0.69–0.97)	407	493	0.80 (0.70–0.92)

ACE = angiotensin-converting enzyme inhibitor treated group; CI = confidence interval; OR = random effects odds ratio; Placebo = placebo treated group.

Figure 1. Odds ratios (**OR**) and their 95% confidence intervals (**CI**) for the endpoint of sudden cardiac death (**SCD**) in each of the 15 individual trials. The overall OR for SCD in patients randomized to ACE inhibitor therapy was 0.80 (95% CI 0.70 to 0.92). Results are shown on a log scale with box width proportional to the sample size.

was of borderline significance ($p = 0.09$). These results justify our a priori choice of the random effects method of estimation.

DISCUSSION

Study results. The present study confirms individual reports showing that treatment with ACE inhibitors reduce overall mortality in patients following acute myocardial infarction. Total mortality is the most definitive endpoint in judging the usefulness of any therapy. The combined studies in this metaanalysis also demonstrated that the reduction in total mortality was mostly the consequence of a reduction in cardiovascular mortality. Further, the present analysis suggests that ACE inhibitors reduce the risk of SCD by about 20% in postmyocardial infarction patients, contributing substantially to the reduction of cardiovascular mortality and, hence, to the reduction of total mortality.

Possible mechanisms of SCD reduction. The mechanisms by which ACE inhibitors prevent SCD have not been fully delineated. However, there are several mechanisms that have been postulated. ACE inhibitors have significant sympatholytic activity (41). Sympathetic activation increases the risk of ventricular tachyarrhythmias. Treatment with an ACE inhibitor may reduce circulating norepinephrine as well as of angiotensin II, which is a facilitator of adrenergic neurotransmission (41). ACE inhibitors may also increase prostacyclin synthesis which reduces local norepinephrine release (42). Improvement in hemodynamic state may also result in sympathetic withdrawal, reducing sympathetically mediated vasoconstriction. As well, the use of ACE inhibitors also provides some protection against potassium depletion since it may offset the potential adverse effects of diuretics. In patients with high blood pressure, diuretics may increase mortality (45). Since many postmyocardial

infarction patients are on diuretics, the potassium sparing effects of the ACE inhibitors may reduce the risk of fatal arrhythmias. Finally, baroreflex sensitivity is increased by ACE inhibition and this may be an important mechanism of reducing sympathetic, and enhancing of vagal tone, potentially reducing SCD (41,43,44).

Effect of ACE inhibitors on remodeling. Attenuation of the remodeling process that follows myocardial infarction is a third way in which ACE inhibitors may be beneficial in reducing the risk of SCD. Remodeling is associated with changes in the function and distribution of cardiac myocytes (46) and in the cardiac interstitium (47). These changes lead to dilatation (3), hypertrophy (48) and to reduced contractility (49) all of which are associated with a poor prognosis (49). Although generally related to alteration in left ventricular function, the resulting abnormalities in the structure and function of the myocardium may contribute to the generation of ventricular arrhythmias. The ACE inhibitors have been shown to attenuate ventricular remodeling (50). Since a reduction in cardiac dilatation may lead to a reduction in ventricular arrhythmias (51), ACE inhibitor therapy may have a role in reducing fatal arrhythmias. Indeed, Søgaard et al. reported less ventricular ectopy in ACE inhibitor treated patients following myocardial infarction (52). In a Holter monitor substudy of SAVE patients, fewer premature ventricular contractions were reported in the ACE inhibitor treated patients (53). In an animal model of chronic myocardial infarction, ACE inhibitor therapy resulted in a reduction of electrophysiologically inducible ventricular arrhythmias (54). Although not directly antiarrhythmic, the reduction in propensity to ventricular arrhythmias afforded by the ACE inhibitors is likely related to attenuation of the remodeling process, reduction in potassium depletion, its sympatholytic properties and other properties that are not well understood.

Effect of ACE inhibitors on recurrent myocardial infarction. Sudden cardiac death may also result from the electrical instability due to coronary occlusion and resultant myocardial infarctions. An autopsy study suggested that about 75% of patients who die suddenly have new thrombus in a coronary artery (55) which suggests a causal role in arrhythmia generation. Chronic ACE inhibitor therapy in patients with left ventricular dysfunction has been shown to reduce the incidence of myocardial infarction in both the SAVE and SOLVD studies (5,12). This prevention of myocardial infarction may be another mechanism by which the ACE inhibitors can reduce SCD. There are mechanisms of SCD other than ventricular arrhythmias, including ventricular rupture. Treatment with ACE inhibitors favorably impacts the ventricular remodeling process (56) and may reduce the risk of ventricular rupture (57).

Limitations. A potential limitation of this study, common to all metaanalyses, is the possibility of publication bias. Such bias is less likely to have influenced this metaanalysis, because SCD was not the primary endpoint of any of the studies. Hence, the fact that a study was negative with respect to reducing SCD is unlikely to have decreased the enthusiasm of authors or reviewers for the study. Also, the clinical trial has become the standard for determining the usefulness of therapeutic interventions. As a result, a randomized trial that bears on the usefulness of a class of drugs as important as ACE inhibitors is likely to be submitted for publication and published, whether positive or negative.

Conclusions. This analysis is consistent with prior reports showing that ACE inhibitor treatment reduces total mortality in postmyocardial infarction patients by reducing cardiovascular mortality. Furthermore, it suggests that the estimated 20% reduction in the odds of SCD by the ACE inhibitors is a significant component of the reduction of cardiovascular death.

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