Chronic nitrate therapy is associated with different presentation and evolution of acute coronary syndromes: insights from 52 693 patients in the Global Registry of Acute Coronary Events†

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Aims

Brief episode(s) of ischaemia may increase cardiac tolerance to a subsequent major ischaemic insult (‘preconditioning’). Nitrates can pharmacologically mimic ischaemic preconditioning in animals. In this study, we investigated whether antecedent nitrate therapy affords protection toward acute ischaemic events using data from the Global Registry of Acute Coronary Events.

Methods and results

The dataset comprised 52 693 patients from 123 centres in 14 countries: 42 138 (80%) were nitrate-naïve and 10 555 (20%) were on chronic nitrates at admission. In nitrate-naïve patients, admission diagnosis was ST-segment elevation myocardial infarction (STEMI) in 41%, whereas 59% presented with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). In contrast, only 18% nitrate users showed STEMI, whereas 82% presented with NSTE-ACS. Thus, among nitrate users clinical presentation was tilted toward NSTE-ACS by more than four-fold, STEMI occurring in less than one of five patients (P < 0.0001). After adjustment (age, sex, medical history, prior therapy, revascularization, previous angina), chronic nitrate use remained independent predictor of NSTE-ACS (OR 1.36; 95% CI 1.26–1.46; P < 0.0001). Furthermore, regardless of presentation, within both STEMI and NSTEMI populations, antecedent nitrate use was associated with significantly lower levels of CK-MB and troponin (P < 0.0001 for all).

Conclusion

In this large multinational registry, chronic nitrate use was associated with a shift away from STEMI in favour of NSTE-ACS and with less release of markers of cardiac necrosis. These findings suggest that in nitrate users acute coronary events may develop to a smaller extent. Randomized, placebo-controlled trials are warranted to establish whether nitrate therapy may pharmacologically precondition the heart toward ischaemic episodes.

Keywords

Ischaemia • Acute coronary syndromes • Preconditioning • Nitrates

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Introduction

Preconditioning is the phenomenon by which brief episodes of ischaemia increase the tolerance of the heart to a subsequent major ischaemic insult. This seemingly paradoxical phenomenon has spurred huge interest. In animal models, preconditioning by brief ischaemia is the most powerful intervention capable of limiting the amount of necrosis due to coronary artery occlusion,1,2 likewise, in the clinical setting, patients experiencing preinfarction angina score significantly better than those in whom myocardial infarction occurs unheralded.3–9

Given the potential beneficial impact of preconditioning, an issue of major clinical relevance is whether its protective effects can be reproduced without having to induce prior ischaemia. Accordingly, the search for preconditioning-mimetic interventions has been extensive. However, few of the many chemicals that are effective in experimental models are suitable for clinical use. A major advance in the field has come with recognition that a fundamental step in the sequence of events eliciting ischaemic preconditioning is represented by activation of nitric oxide (NO) synthase, with its attendant production of NO.10–13 This has enabled the development of design-specific experimental protocols which have demonstrated that exogenous administration of NO donors is capable of reproducing the beneficial effects of ischaemic preconditioning. In this respect, pretreatment with nitrates markedly reduces myocardial infarct size induced by subsequent coronary artery occlusion in animals,14–17 and it significantly reduces indices of myocyte injury in patients subjected to percutaneous transluminal coronary angioplasty.18 Importantly, nitrates share with ischaemic preconditioning common mechanisms of action, including protein kinase C (PKC)-dependent signalling,19–23 opening of KATP channels,24–27 and changes in myocardial redox status.16,17,28,29

Because of their ease of use and favourable safety profile, nitrates are the mainstay therapy of stable coronary artery disease. Thus, it is important to know whether nitrates could also be exploited clinically as inducers of ‘pharmacological preconditioning’ toward myocardial infarction. Randomized clinical trials are necessary to firmly test this hypothesis: however, this requires major logistic and economic efforts. Accordingly, it may be relevant to gain better insights into this issue before embarking in specifically designed randomized clinical trials.

As a means to get additional information in this respect, in the present study, we explored whether antecedent nitrate therapy affords cardiac protection toward a major ischaemic episode. To this goal, we used data from the Global Registry of Acute Coronary Events (GRACE), a large, multinational registry of patients hospitalized with an acute coronary syndrome (ACS),30,31 to compare patients on chronic nitrate therapy at the time of hospital admission with nitrate-naïve individuals.

Methods

GRACE is a prospective registry designed to reflect an unselected population of patients with ACS, irrespective of geographic region. A total of 123 hospitals located in 14 countries in North and South America, Europe, Australia, and New Zealand have contributed data.30,31 Where required, study investigators received approval from their local hospital ethics or institutional review board for the conduct of this registry.

Patients (≥18 years) admitted with a presumptive diagnosis of ACS were potentially eligible for inclusion. Eligibility criteria were a clinical history of ACS, accompanied by at least one of the following: electrocardiographic changes consistent with ACS; serial increases in biochemical markers of cardiac necrosis [creatinine kinase (CK)-MB, creatine phosphokinase, or troponin], documented coronary artery disease. Patients with non-cardiovascular causes for the clinical presentation (e.g., trauma, surgery, aortic aneurysm) were excluded, as were patients in whom initial diagnosis of ACS was not confirmed at discharge (see Results).

To enrol an unselected population of patients, sites were encouraged to recruit the first 10–20 consecutive eligible patients each month. Regular audits were performed at all participating hospitals. Data were collected by trained study coordinators using standardized case report forms. Demographic characteristics, medical history, presenting symptoms, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables, clinical diagnoses, and hospital complications and outcomes were used. Patients were diagnosed with ST-segment elevation myocardial infarction (STEMI) when they had presumed new ST-segment elevation ≥1 mm in any location or new left bundle-branch block (LBBB) on the index ECG, with at least one positive cardiac biochemical marker of necrosis. In cases of non-STEMI (NSTEMI), at least one positive cardiac biochemical marker of necrosis had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis in each hospital’s laboratory were within normal range. Positivity of markers of necrosis at presentation was established based on blood samples taken on admission, while the highest value measured on blood samples taken within 24 h was considered peak release (visit www.outcomes.org/grace for full definitions).

Standardized core case records were accessed at the Center for Outcomes Research to retrieve information on patient demographics, and clinical and treatment characteristics. Baseline characteristics, admission and discharge diagnoses, and outcome data were compared between patients on chronic nitrate therapy at the time of the index event and those who were nitrate-naïve. Chronic nitrate use was defined as medication routinely taken at home and started at least 7 days prior to index event. ‘Previous angina’ was defined if the patient (on a separate occasion) had a diagnosis of angina by a physician.

Statistical analysis

Unless specified otherwise, numeric variables are expressed as medians (25th–75th percentile). Univariate comparisons of patient demographics, medical history, and laboratory data were made using χ2 or Wilcoxon rank sum tests. All tests were two-sided and considered significant at P < 0.05. Multivariable logistic regression was used to assess the relationship between chronic nitrate treatment and new ST-elevation (STE) or LBBB, discharge diagnosis of STEMI, and in-hospital death; all regression models were built using backward selection. The models controlled for medical history (including all relevant cardiovascular events or procedures and history of angina), GRACE risk score variables at presentation (Killip class, cardiac arrest, initial enzymes, systolic blood pressure, pulse, age, creatinine),32 and any chronic drug use (including other antianginal medications). The model for in-hospital mortality additionally controlled for in-hospital drug use, percutaneous coronary intervention, reperfusion with fibrinolytics, coronary artery bypass graft surgery. In each case,
variables significant at \( P < 0.05 \) were kept in the final model. Statistical analysis was performed using SAS software (version 9.1, SAS Institute, Cary, NC, USA).

Results

The initial dataset for this study comprised 66,456 patients admitted for an ACS between April 1999 and June 2007. Information about chronic nitrate use was not available in 590 patients; of the remaining individuals, a diagnosis of ACS was confirmed in 60,868. A total of 8175 had been transferred from other non-GRACE hospitals and were therefore excluded from the analysis. The final analysis was performed in 52,693 patients, of whom 42,138 (80%) were nitrate-naive at admission and 10,555 (20%) were on chronic nitrate therapy.

Patients on chronic nitrate therapy were older and, on average, their clinical profile was indicative of more advanced atherosclerotic disease (Table 1). As a consequence, the risk profile calculated according to the GRACE risk score was significantly higher in patients who were nitrate-naive compared with chronic nitrate users (Table 1, \( P < 0.0001 \)).

Clinical presentation at admission

In nitrate-naive patients, STE/LBBB was the admission diagnosis in 17,478 (41%), whereas 24,660 (59%) presented with non-ST-elevation (NSTE)-ACS (Figure 1A). In contrast, of those on chronic nitrate therapy 1940 (18%) presented with STE/LBBB and 8615 (82%) had an admission diagnosis of NSTE-ACS, i.e. in nitrate users STE/LBBB was present in less than one in five patients (Figure 1A; \( P < 0.0001 \)).

Discharge diagnosis

The lower prevalence of STEMI at admission among chronic nitrate users was confirmed when data were analysed according to discharge diagnosis (i.e. when admission diagnosis was corroborated by other clinical data and by the release of biochemical markers of cardiac necrosis during hospitalization; Figure 1B). STEMI occurred in 39% of nitrate-naive patients vs. 16% of chronic nitrate users (\( P < 0.0001 \); Figure 1B). In contrast, prevalence of unstable angina was significantly higher in nitrate-naive than in chronic nitrate users (51% vs. 28%; \( P < 0.0001 \); Figure 1B). Accordingly, rates of antecedent chronic nitrate use varied according to discharge diagnosis (\( P < 0.0001 \); Figure 2).

Table 1  Patient population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nitrate-naive (( n = 42,138 ))</th>
<th>Chronic nitrate users (( n = 10,555 ))</th>
<th>( P )-value</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years) (IQR)</td>
<td>66 (55, 75)</td>
<td>72 (62, 79)</td>
<td>(&lt; 0.0001 )</td>
<td>130 (0.2)</td>
</tr>
<tr>
<td>Men</td>
<td>28,507 (68)</td>
<td>6493 (62)</td>
<td>(&lt; 0.0001 )</td>
<td>256 (0.5)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>19,581 (47)</td>
<td>8665 (83)</td>
<td>(&lt; 0.0001 )</td>
<td>239 (0.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10,232 (24)</td>
<td>5934 (57)</td>
<td>(&lt; 0.0001 )</td>
<td>253 (0.5)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3326 (8.0)</td>
<td>1639 (16)</td>
<td>(&lt; 0.0001 )</td>
<td>436 (0.8)</td>
</tr>
<tr>
<td>TIA/stroke</td>
<td>3115 (7.5)</td>
<td>1341 (13)</td>
<td>(&lt; 0.0001 )</td>
<td>415 (0.8)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2669 (6.4)</td>
<td>1351 (13)</td>
<td>(&lt; 0.0001 )</td>
<td>237 (0.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9741 (23)</td>
<td>3414 (33)</td>
<td>(&lt; 0.0001 )</td>
<td>263 (0.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24,779 (59)</td>
<td>7770 (74)</td>
<td>(&lt; 0.0001 )</td>
<td>297 (0.6)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>18,598 (44)</td>
<td>6391 (61)</td>
<td>(&lt; 0.0001 )</td>
<td>415 (0.8)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3379 (8.1)</td>
<td>2248 (22)</td>
<td>(&lt; 0.0001 )</td>
<td>428 (0.8)</td>
</tr>
<tr>
<td>Coronary angiogram diagnostic for CAD</td>
<td>10,297 (25)</td>
<td>5900 (58)</td>
<td>(&lt; 0.0001 )</td>
<td>1026 (2.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2906 (7.0)</td>
<td>1307 (13)</td>
<td>(&lt; 0.0001 )</td>
<td>482 (0.9)</td>
</tr>
<tr>
<td>Smoker</td>
<td>24,076 (57)</td>
<td>5546 (53)</td>
<td>(&lt; 0.0001 )</td>
<td>279 (0.5)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>6013 (14)</td>
<td>3213 (31)</td>
<td>(&lt; 0.0001 )</td>
<td>320 (0.6)</td>
</tr>
<tr>
<td>CABG</td>
<td>3942 (9.4)</td>
<td>2689 (26)</td>
<td>(&lt; 0.0001 )</td>
<td>308 (0.6)</td>
</tr>
<tr>
<td>Positive stress test</td>
<td>3694 (8.9)</td>
<td>2050 (20)</td>
<td>(&lt; 0.0001 )</td>
<td>602 (1.1)</td>
</tr>
<tr>
<td>Major surgery</td>
<td>1648 (3.9)</td>
<td>54 (5.7)</td>
<td>(&lt; 0.0001 )</td>
<td>215 (0.4)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>408 (1.0)</td>
<td>201 (1.9)</td>
<td>(&lt; 0.0001 )</td>
<td>224 (0.4)</td>
</tr>
<tr>
<td>Median GRACE risk score (IQR)</td>
<td>128 (105, 155)</td>
<td>131 (106, 159)</td>
<td>(&lt; 0.0001 )</td>
<td>5744 (11)</td>
</tr>
</tbody>
</table>

Values given as \( n \) (%) unless otherwise stated. CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; TIA, transient ischaemic attack.
Overall, 22,926 (44%) patients had positive biomarkers at admission. Almost half (48%) of the nitrate-naive patients had positive markers vs. 31% of chronic nitrate users ($P < 0.0001$): this finding was consistent for all markers tested (Table 2). Importantly, this difference remained unchanged ($P < 0.0001$) for the nitrate-naive patients and positive markers remained significantly higher in nitrate-naive at admission ($P < 0.0001$). Overall, 22.96% (44%) patients had positive biomarkers at admission.

### Table 2: Release of markers of myocyte necrosis on admission; patients grouped according to ECG diagnosis

<table>
<thead>
<tr>
<th>Marker</th>
<th>STE/LBBB Nitrate Naive</th>
<th>STE/LBBB Nitrate Users</th>
<th>NSTE-ACS Nitrate Naive</th>
<th>NSTE-ACS Nitrate Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>19,678 (48)</td>
<td>3248 (28)</td>
<td>930 (48)</td>
<td>690 (44)</td>
</tr>
<tr>
<td>CPK $&gt; 2 \times$ ULN</td>
<td>5994 (17)</td>
<td>1269 (9)</td>
<td>369 (14)</td>
<td>171 (12)</td>
</tr>
<tr>
<td>Troponin</td>
<td>756 (3)</td>
<td>3519 (24)</td>
<td>2318 (27)</td>
<td>1885 (20)</td>
</tr>
</tbody>
</table>

Any marker, $P < 0.0001$. CK-MB, 27,916 (53); CPK, 8467 (16); troponin, 13,337 (25)—data are given as missing $n$. CK, creatine kinase; CPK, creatine-phosphokinase; LBBB, left bundle-branch block; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STE, ST-elevation; ULN, upper limit of normal.
diagnosis, i.e. even within NSTE-ACS patients chronic nitrate use was associated with significantly lower release of markers.

Of patients with data available on cardiac biomarkers during hospitalization (n = 28 075), 83% were nitrate-naive, and 17% were chronic nitrate users. The clinical characteristics of patients in these subgroups were similar to those of nitrate-naive patients and chronic nitrate users in the entire dataset (data not shown).

In the STEMI subgroup, chronic nitrate use was associated with significantly lower levels of CK-MB and troponin vs. nitrate-naive patients (P,0.0001 for all; Figure 3A and B). Total CK levels were also significantly lower in nitrate users compared with nitrate-naive patients (410.5 vs. 1016.0 U; P,0.0001). Again, within the NSTEMI subgroup, patients who were taking chronic nitrates showed significantly lower peak levels of markers during hospitalization compared with nitrate-naive patients (Figure 3B); total CK levels were also significantly lower in nitrate users compared with nitrate-naive patients (175.0 vs. 276.0 U; P < 0.0001).

**Mortality**

Unadjusted hospital mortality rate for all ACS was 4.9% for nitrate-naive patients and 4.9% in chronic nitrate users (P = 0.95). When mortality was corrected for the different clinical profiles, the OR for hospital death for chronic nitrate users with STE-ACS vs. nitrate-naive patients was 1.12 (95% CI 0.89–1.41; P=NS); likewise, the OR for hospital death for chronic nitrate users with NSTE-ACS vs. nitrate-naive patients was 0.95 (95% CI 0.79–1.14; P=NS).

**Discussion**

The present study sought to provide an indication as to whether prior chronic nitrate therapy confers cardioprotection in patients suffering an ACS. In this multinational, unselected cohort of over 50 000 patients, we observed that chronic nitrate users at the time of the index coronary event were much less likely to be admitted for STEMI compared with patients who were nitrate-naive. Nitrate users were also more likely to be discharged with a diagnosis of unstable angina rather than myocardial infarction. Furthermore, chronic nitrate use was associated with significantly lower levels of cardiac markers of necrosis during hospital stay. Together, these findings indicate that chronic nitrate users tend to develop a smaller extent of myocardial necrosis, or no necrosis altogether, in response to an episode of ACS. Coupled with solid background data in animal models, our observation strongly suggests that it may be worth designing randomized clinical trials to directly address the issue of nitrate-mediated preconditioning in patients.

Brief ischaemic episodes can precondition the heart (i.e. make it more tolerant to subsequent major ischaemic insults). Release of endogenous NO by NO-synthase is a key event in this phenomenon, and it accounts for activation of the biochemical
cascade that, through changes in myocardial redox status, PKC-dependent signalling, and opening of KATP channels, leads to myocyte protection. Experimentally, this protective phenotype can be pharmacologically mimicked—in the absence of prior ‘preconditioning’ ischaemia—by pretreatment with nitrates and other NO donors or with drugs that increase NO availability. In fact, involvement of NO has been postulated as the ultimate mechanism of many infarct-sparing therapies.

In contrast to the wealth of convincing, rigorously performed animal studies stands the paucity of information as to whether the preconditioning-mimetic action of NO donors can be successfully exploited in patients. In one study, prior administration of nitroglycerin significantly reduced indices of myocyte injury in patients undergoing percutaneous transluminal coronary angioplasty; preconditioning-mimetic actions of nitroglycerin were also demonstrated in patients with stable angina undergoing exercise stress tests. However, whether pretreatment with nitrates can afford myocardial protection in patients who would eventually suffer an acute coronary event remains unknown.

In the present study, we used data from over 52,000 unselected patients with an ACS in the GRACE registry, which consistently point to a possible preconditioning-mimetic action of chronic nitrate therapy. First, STEMI (thought to reflect chiefly transmural necrosis) was much more prevalent among patients who were nitrate-naïve, whereas NSTEMI (typically associated with a smaller extent of myocyte death) largely prevailed among chronic-nitrate users. Second, episodes of ACS that did not evolve to myocardial infarction (i.e. unstable angina) were significantly more likely to occur in chronic-nitrate users. Third, nitrate users showed significantly lower release of biochemical markers of myocyte necrosis: this was not a passive reflection of the fact that in this population the ACS episode more frequently remained confined to unstable angina (in which no release is expected to occur), because the difference persisted when data were analysed within the specific conditions of STEMI and NSTEMI, in both cases favouring nitrate users. Collectively, these findings concur to suggest that chronic-nitrate therapy may exert a beneficial effect, akin to a pharmacological preconditioning toward ischaemia, which manifests with a smaller extent of myocardial necrosis in response to an acute coronary event.

Limitations/confounding factors
Like all registries, the results of this study have limitations: most notably, patients were not randomly assigned to nitrates. Also, nitrate users had a worse cardiovascular risk profile than nitrate-naïve patients: this difference might have affected our findings, as myocardial injury might be less pronounced in these patients, because chronic angina or previous revascularization may have increased collateral blood flow or because drugs favourably impacting ACS were already being taken. However, it is also plausible that patients in whom atherosclerotic disease is more severe and/or more advanced, or who suffer from concomitant diseases, would be prone to greater injury during an ischaemic episode; this might also explain why mortality was similar in both groups. We ran multivariable analyses to account for these and other variables; after correcting for potential confounders, nitrate use remained an independent negative predictor for STEMI.

Could better outcome in nitrate users be due to other beneficial effects, unrelated to preconditioning? One obvious consideration is that nitrates are coronary vasodilators. This property may translate into myocardial protection, as shown by earlier clinical trials. However, current guidelines do not advocate nitrate use to improve myocardial protection and prognosis, during either STEMI or UA/NSTEMI.

A possible consequence of lack of randomization is a selection bias in nitrate prescription, these agents being preferentially prescribed to patients who have more extensive CAD. As those patients may have had multiple infarcts, we might only see those with small residual ischaemic territories, because patients with larger territories would die before reaching hospital. In principle, this phenomenon might influence data relative to STEMI, but it should not apply to UA/NSTEMI, as in this latter condition, the amount of irreversibly injured myocardium tends to be substantially small; hence, pre-hospital death because of cardiogenic shock or massive LV deterioration should not be an issue. Indeed, also within the UA/NSTEMI subgroup, nitrate users still showed less release of CK and troponin, consistent with the hypothesis that consequences of an ischaemic episode tend to be less severe in prior nitrate users.

Another possible selection bias linked to nitrate prescription could happen if one assumes that nitrate use is a ‘marker’ of cardiac disease. Hence, it may be speculated that nitrate users are (more) aware of their condition of cardiac patients, and therefore more likely to seek medical advice, and/or to seek it earlier, than patients not taking nitrates.

Finally, one should consider possible dis-homogeneity in the use of sulfonylureas. These agents may inhibit ischaemic preconditioning via KATP channel blockade. In our registry, chronic nitrate users were 24% of patients on oral anti-diabetic drugs (n = 1576), whereas 76% (n = 4937) were nitrate-naïve. This compares favourably with the relative proportion of 20% nitrate users in the whole dataset. The fact that among patients taking sulfonylureas the proportion of nitrate users was greater than in the overall population of our study is important, given the possibility that sulfonylureas might have worked against preconditioning, because if anything nitrate users should have done worse.

For these various reasons, and because of the non-randomized nature of the observation, our data should be considered as hypothesis-generating, encouraging toward designing specific clinical trials to ultimately test the hypothesis.

Clinical implications
Nitrates have remained the mainstay therapy for stable coronary artery disease for many years. More recently, use of chronic-nitrate therapy has declined because of the diminished appeal of drug therapy for stable angina in the era of revascularization. Moreover, use of nitrates has been questioned due to their potential as inducers of oxidant stress. However, oxidants can actually be mediators of preconditioning. Thus, given their ease of use, lack of side effects, and low cost, demonstration of nitrates capability to act as pharmacological inducers of preconditioning may spark renewed interest in these drugs.
Conclusions

In this large, multinational, cohort study of patients with ACS, chronic nitrate therapy was associated with multiple indications of reduced severity of myocardial injury in response to an acute coronary event. Randomized clinical trials should test the hypothesis that nitrate therapy may pharmacologically precondition the heart toward a subsequent major ischaemic episode, thereby reducing the extent of myocardial infarction.

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Conflict of interest: none declared.

Appendix

GRACE participants


References

Chronic nitrate therapy is associated with different presentation and evolution of ACS


