A population-based study of the drug interaction between clopidogrel and angiotensin converting enzyme inhibitors

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
• Clopidogrel can inhibit carboxylesterase 1, which is responsible for the bioactivation of prodrug ACE inhibitors.

WHAT THIS STUDY ADDS
• In subjects receiving clopidogrel following acute myocardial infarction, use of a prodrug ACE inhibitor (ramipril or perindopril) was not associated with an increased risk of adverse cardiovascular events or death relative to lisinopril.
• These findings suggest that the recently described interaction between clopidogrel and prodrug ACE inhibitors is of little clinical relevance.

AIMS
Clopidogrel and angiotensin converting enzyme (ACE) inhibitors are commonly co-prescribed drugs. Clopidogrel inhibits carboxylesterase 1 (CES1), the enzyme responsible for converting prodrug ACE inhibitors (such as ramipril and perindopril) to their active metabolites. The clinical implications of this potential drug interaction are unknown. The clinical consequences of the potential drug interaction between clopidogrel and prodrug ACE inhibitors were examined.

METHODS
We conducted a nested case–control study of Ontarians aged 66 years and older treated with clopidogrel between September 1 2003 and March 31 2013 following acute myocardial infarction. Cases were subjects who died or were hospitalized for reinfarction or heart failure in the subsequent year, and each was matched with up to four controls. The primary analysis examined whether use of the prodrug ACE inhibitors ramipril or perindopril was more common among cases than use of lisinopril, an active ACE inhibitor.

RESULTS
Among 45 918 patients treated with clopidogrel following myocardial infarction, we identified 4203 cases and 14 964 controls. After adjustment, we found no association between the composite outcome and use of perindopril (adjusted odds ratio (aOR) 0.94, 95% confidence interval (CI) 0.76, 1.16) or ramipril (aOR 0.97, 95% CI 0.80, 1.18), relative to lisinopril. Secondary analyses of each element of the composite outcome yielded similar findings.
CONCLUSIONS
Following myocardial infarction, use of clopidogrel with ACE inhibitors activated by CES1 is not associated with an increased risk of adverse cardiovascular outcomes relative to lisinopril. These findings suggest that the recently described drug interaction between clopidogrel and prodrug ACE inhibitors is of little clinical relevance.

Introduction
Angiotensin converting enzyme (ACE) inhibitors are among the most widely prescribed medications in the world, with more than 160 million prescriptions dispensed in the United States in 2011 [1]. They are indicated in the management of various conditions including hypertension, diabetes mellitus, heart failure and left ventricular systolic dysfunction. Their use following acute myocardial infarction reduces the risk of hospitalization for heart failure, reinfarction, and mortality [2–5]. Clopidogrel is a thienopyridine anti-platelet agent dispensed more than 20 million times each year in the United States alone [6]. Like ACE inhibitors, it is widely prescribed to patients following acute myocardial infarction [4, 5]. When added to acetylsalicylic acid in patients with myocardial infarction, clopidogrel decreases the risk of adverse cardiovascular events including reinfarction and mortality [4, 5].

Some data suggest that the available ACE inhibitors are equally effective following acute myocardial infarction [7, 8]. However, important pharmacologic differences exist among the drugs in this class. Most commonly prescribed ACE inhibitors (including ramipril, trandolapril, enalapril and perindopril) are prodrugs that are de-esterified to active metabolites (ramiprilat, trandolaprilat, enalaprilat and perindoprilat, respectively) by the enzyme carboxylesterase 1 (CES1), an enzyme highly expressed in liver and increasingly appreciated as an important factor in drug metabolism [9–12]. In contrast, lisinopril and captopril are active ACE inhibitors that require no such bio-activation [13]. Genetic variation in CES1 has been shown to influence drug metabolism and may influence the antihypertensive effects of ACE inhibitors such as imidapril [11, 14–18].

Importantly, CES1 can be inhibited by other medications and substrates, including clopidogrel [19–22]. Clopidogrel-mediated inhibition of this enzyme has been shown to interfere with the bio-activation of several prodrugs, including oseltamivir and others [19, 20]. Recent findings of Kristensen and colleagues also suggest that ACE inhibitors may competitively inhibit CES1, thereby shunting clopidogrel towards CYP-mediated bioactivation and increasing the concentration of active metabolites in vitro [23]. In a population-based sub-study, they found that ACE inhibitors were associated with an increased risk of haemorrhage and adverse cardiovascular events (including cardiovascular death, stroke or reinfarction) in those simultaneously receiving clopidogrel following acute myocardial infarction [23]. However, their primary conclusions compare clopidogrel-treated patients with those not receiving clopidogrel, increasing the possibility of selection bias.

Despite the co-prescription of ACE inhibitors and clopidogrel to millions of patients each year, the clinical relevance of this novel drug interaction is poorly characterized. We examined the clinical consequences of the potential drug interaction between clopidogrel and prodrug ACE inhibitors in a large population.

Methods
Setting and design
We conducted a population-based nested case–control study of Ontario residents aged 66 years or older who commenced treatment with clopidogrel following hospitalization for acute myocardial infarction between September 1 2003 and March 31 2013. These individuals had universal access to hospital care, physicians’ services and drug coverage. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada. The study design is depicted in Figure 1.

Data sources
We used Ontario’s administrative health databases which are held securely in linkable files without any direct personal identifiers. We identified prescription drug claims...
using the Ontario Drug Benefit Database, which includes records of prescriptions dispensed to all Ontarians aged 65 years or older. We obtained hospitalization data from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which contains detailed clinical information regarding all hospital admissions, and data on emergency department visits from the CIHI National Ambulatory Care Reporting System. We identified patients with hypertension, diabetes and congestive heart failure using validated disease-specific databases [24–26]. Demographic and mortality data were obtained from the Ontario Health Insurance Plan Registered Persons Database, a registry of all Ontario residents with publically-funded health insurance, and physicians’ services were identified using OHIP physician claims data. These databases were linked in an anonymous fashion using encrypted Ontario health card numbers, and are routinely used to study drug safety [27–32].

Study subjects
We identified individuals who commenced treatment with clopidogrel following hospital discharge for acute myocardial infarction, defined as receipt of their first prescription on the day before discharge or within 7 days thereafter. For each patient, we defined a period of up to 1 year of continuous clopidogrel use, beginning with the first clopidogrel prescription and ending with death, hospitalization for heart failure or reinfarction, discontinuation of treatment or the end of the study period, whichever occurred first. Patients were deemed to have discontinued clopidogrel if the interval between successive prescriptions exceeded twice the days supplied by the preceding prescription. In such instances, observation continued until the expiry of the first of these two prescriptions. We did not study patients during their first year of eligibility for prescription drug coverage (age 65 years) to avoid incomplete medication records. To focus on patients newly treated with clopidogrel, we excluded those with any prior use of the drug.

Within the cohort of continuous clopidogrel users, we defined cases as subjects who died or were readmitted to hospital for reinfarction or heart failure within 1 year. We identified hospital admissions using previously validated International Classification of Disease and Related Health Problems (ICD), 10th revision codes for acute myocardial infarction (I21) and heart failure (I50) [25, 33]. We designated the index date as the date of death or hospital admission for reinfarction or heart failure (Figure 1). For patients with multiple such admissions during follow-up, only the first event was considered in the analysis. For each case, we selected up to four controls from the same cohort of clopidogrel-treated patients, matching on the date of index hospitalization, age (within 1 year), gender, calendar year of clopidogrel initiation, and the time between cohort entry and index date (within 30 days). We allowed each control to be matched to only one case. When fewer than four controls were matched to a case, we used only those controls and maintained the matching process. We excluded cases that could not be matched to at least one control, and controls were permitted to become cases at a later date.

We limited the analyses to cases and controls who received a prescription for one of ramipril, perindopril or lisinopril in the 60 days preceding the index date. We selected these agents because they represent the most commonly prescribed ACE inhibitors in Ontario, thereby allowing us to explore the drug interaction of interest while minimizing the number of comparisons. We excluded those who received any other ACE inhibitor, those who received an angiotensin receptor blocker, and those who received more than one ACE inhibitor in the same 60 day period.

Statistical analysis
We used standardized differences to compare baseline characteristics of cases and controls. A standardized difference less than 0.1 indicates good balance between cases and controls for a given covariate [34]. We used conditional logistic regression to estimate the odds ratio and 95% confidence interval (CI) for the association between the composite outcome (death or hospitalization for heart failure or reinfarction) and exposure to either ramipril or perindopril, using lisinopril as the reference group. We adjusted for all variables with a standardized difference exceeding 0.1 between cases and controls. In a secondary analysis, we applied the same analytical approach to each component of the primary outcome separately. To test the sensitivity of our findings, we repeated our analyses using a 100 day look-back period for ACE inhibitor exposure.

All analyses used a two-sided type I error rate of 0.05 as the threshold for statistical significance and were performed at the Institute for Clinical Evaluative Sciences (www.ices.on.ca) using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

Results
During the 10 year study period, we identified 45 918 patients aged 66 years or older who commenced clopidogrel following hospital discharge for acute myocardial infarction. Within this cohort, 9814 subjects died or were hospitalized for reinfarction or heart failure within 1 year while receiving clopidogrel. Of these, 4303 cases received one of lisinopril, ramipril or perindopril in the 60 days preceding their index date. The majority of cases (n = 4203, 97.7%) were matched to at least one control (n = 14 964). As expected, case subjects displayed more comorbid illness and greater use of medications for cardiovascular disease and diabetes. The characteristics of case and control subjects are outlined in Table 1.

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Table 1
Characteristics of study subjects

| Variable                                      | Cases n = 4203 | Controls n = 14 964 | Standardized difference |
|-----------------------------------------------|----------------|---------------------|-------------------------|
| Age (years), median (IQR)                     |                |                     |                         |
| 66–74                                         | 1177 (28.0)    | 4741 (31.7)         | 0.08                    |
| 75–84                                         | 1849 (44.0)    | 7041 (47.1)         | 0.06                    |
| 85+                                           | 1177 (28.0)    | 3182 (21.3)         | 0.16                    |
| Female, n (%)                                 | 1965 (46.8)    | 6772 (45.3)         | 0.03                    |
| Income quintile, n (%)                        |                |                     |                         |
| 1                                             | 1019 (24.2)    | 3192 (21.3)         | 0.07                    |
| 2                                             | 908 (21.6)     | 3171 (21.2)         | 0.01                    |
| 3                                             | 759 (18.1)     | 2940 (19.6)         | 0.04                    |
| 4                                             | 775 (18.4)     | 2857 (19.1)         | 0.02                    |
| 5                                             | 723 (17.2)     | 2755 (18.4)         | 0.03                    |
| Missing                                       | 19 (0.5)       | 49 (0.3)            | 0.02                    |
| Residence in long term care facility, n (%)   |                |                     |                         |
| 1                                             | 463 (11.0)     | 606 (4.0)           | 0.31                    |
| Charlson score, n (%)                         |                |                     |                         |
| 1                                             | 902 (21.5)     | 7051 (47.1)         |                         |
| 2                                             | 3301 (78.5)    | 7913 (52.9)         | 0.53                    |
| Coronary interventions, n (%)                 |                |                     |                         |
| Percutaneous coronary intervention            | 1540 (36.6)    | 8725 (58.3)         | 0.44                    |
| Coronary artery bypass graft                  | 146 (3.5)      | 618 (4.1)           | 0.03                    |
| Comorbidities in prior 5 years, n (%)         |                |                     |                         |
| Hypertension                                  | 4028 (95.8)    | 13 795 (92.2)       | 0.14                    |
| Diabetes                                      | 4041 (96.1)    | 14 031 (93.8)       | 0.10                    |
| Stroke or transient ischaemic attack          | 334 (7.9)      | 643 (4.3)           | 0.17                    |
| Myocardial infarction                         | 3965 (94.3)    | 14 366 (96.0)       | 0.08                    |
| Peripheral vascular disease                   | 325 (7.7)      | 556 (3.7)           | 0.19                    |
| Chronic liver disease                         | 163 (3.9)      | 391 (2.6)           | 0.08                    |
| Chronic kidney disease                        | 937 (22.3)     | 1710 (11.4)         | 0.32                    |
| Congestive heart failure                      | 3,605 (85.8)   | 13 211 (88.3)       | 0.08                    |
| Atrial fibrillation                           | 964 (22.9)     | 2003 (13.4)         | 0.27                    |
| Cardiac dysrhythm                             | 1298 (30.9)    | 3031 (20.3)         | 0.26                    |
| Angina                                        | 2808 (66.8)    | 11 15 (74.3)        | 0.17                    |
| Cardiomyopathy                                | 79 (1.9)       | 151 (1.0)           | 0.08                    |
| Number of prescription drugs, median (IQR)*   | 16 (12–21)     | 12 (9–17)           | 0.59                    |
| Medication use in preceding 90 days, n (%)    |                |                     |                         |
| Amiodarone                                    | 242 (5.8)      | 476 (3.2)           | 0.14                    |
| Aspirin and other anti-platelet drugs         | 431 (10.3)     | 1560 (10.4)         | 0.01                    |
| β-adrenoceptor blockers                       | 3474 (82.7)    | 12 093 (80.8)       | 0.05                    |
| Calcium channel blockers                      | 1342 (31.9)    | 3733 (24.9)         | 0.16                    |
| Digoxin                                       | 462 (11.0)     | 698 (4.7)           | 0.27                    |
| Fibrates                                      | 69 (1.6)       | 200 (1.3)           | 0.03                    |
| Insulin                                       | 528 (12.6)     | 851 (5.7)           | 0.27                    |
| Loop diuretics                                | 2243 (53.4)    | 3793 (25.3)         | 0.62                    |
| Nitrates                                      | 2663 (63.4)    | 8002 (53.5)         | 0.20                    |
| Non-ASA NSAIDs                                | 422 (10.0)     | 1489 (10.0)         | 0.00                    |
| Novel oral anticoagulants                     | 7 (0.2)        | 26 (0.2)            | 0.00                    |
| Non-loop diuretics                            | 606 (14.4)     | 2298 (15.4)         | 0.03                    |
| Oral glucose-lowering drugs                   | 1054 (25.1)    | 2505 (16.7)         | 0.22                    |
| Other antihypertensive agents                 | 71 (1.7)       | 112 (0.7)           | 0.10                    |
| Spironolactone                                | 423 (10.1)     | 676 (4.5)           | 0.24                    |
| Statins                                       | 3648 (86.8)    | 13 649 (91.2)       | 0.15                    |
| Warfarin                                      | 631 (15.0)     | 1387 (9.3)          | 0.19                    |

ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; IQR, interquartile range. *In prior year.
In the primary analysis, we found that compared with clopidogrel recipients receiving lisinopril, no increased risk of death, heart failure or reinfarction was apparent among those receiving perindopril (adjusted odds ratio 0.94, 95% CI 0.76, 1.16; Table 2) or ramipril (adjusted odds ratio 0.97, 95% CI 0.80, 1.18; Table 2). In a secondary analysis examining each component of the primary outcome individually, we found no significant association between death or readmission for either reinfarction or heart failure and use of perindopril or ramipril in the preceding 60 days, relative to lisinopril (Table 3). Analyses in which the look-back period for ACE inhibitor use was extended to 100 days yielded similar findings.

**Table 2**
Risk of death or hospitalization for heart failure or reinfarction during clopidogrel therapy, by ACE inhibitor

|                      | Cases   | Controls | Adjusted odds ratio (95% CI) |
|----------------------|---------|----------|-----------------------------|
| **Primary analysis** |         |          |                            |
| Lisinopril           | 183 (4.4) | 504 (3.4) | 1.00 (reference)            |
| Perindopril          | 703 (16.7) | 2,763 (18.5) | 0.94 (0.76, 1.16)          |
| Ramipril             | 3317 (78.9) | 11,697 (78.2) | 0.97 (0.80, 1.18)          |
| **Secondary analysis** |         |          |                            |
| Reinfarction         | n = 1832 | n = 6976 | 1.00 (reference)           |
| Lisinopril           | 82 (4.5) | 234 (3.4) | 1.00 (reference)           |
| Perindopril          | 314 (17.1) | 1,299 (18.6) | 1.10 (0.81, 1.50)          |
| Ramipril             | 1436 (78.4) | 5,443 (78.0) | 1.10 (0.83, 1.47)          |
| Heart failure        | n = 2069 | n = 7771 | 1.00 (reference)           |
| Lisinopril           | 90 (4.3) | 294 (3.8) | 1.00 (reference)           |
| Perindopril          | 328 (15.9) | 1,353 (17.4) | 1.02 (0.75, 1.40)          |
| Ramipril             | 1651 (79.8) | 6,124 (78.8) | 1.10 (0.83, 1.45)          |
| All-cause mortality  | n = 1953 | n = 7234 | 1.00 (reference)           |
| Lisinopril           | 78 (4.0) | 228 (3.2) | 1.00 (reference)           |
| Perindopril          | 306 (15.7) | 1,394 (19.3) | 0.83 (0.59, 1.18)          |
| Ramipril             | 1569 (80.3) | 5,612 (77.6) | 0.97 (0.70, 1.34)          |

*Adjusted for age, income quintile, long term care residence, Charlson comorbidity score, hypertension, diabetes, stroke, peripheral vascular disease, chronic kidney disease, percutaneous coronary intervention, cardiac dysrhythmia, angina, total number of distinct drugs, amiodarone, calcium channel blockers, digoxin, insulin, loop diuretics, nitrates, oral glucose-lowering drugs, other antihypertensive agents, spironolactone, statins and warfarin.

**Table 3**
Risk of each outcome among clopidogrel recipients, by ACE inhibitor

|                      | Cases   | Controls | Adjusted odds ratio (95% CI) |
|----------------------|---------|----------|-----------------------------|
| **Secondary analysis** |         |          |                            |
| Reinfarction         | n = 1832 | n = 6976 | 1.00 (reference)           |
| Lisinopril           | 82 (4.5) | 234 (3.4) | 1.00 (reference)           |
| Perindopril          | 314 (17.1) | 1,299 (18.6) | 1.10 (0.81, 1.50)          |
| Ramipril             | 1436 (78.4) | 5,443 (78.0) | 1.10 (0.83, 1.47)          |
| Heart failure        | n = 2069 | n = 7771 | 1.00 (reference)           |
| Lisinopril           | 90 (4.3) | 294 (3.8) | 1.00 (reference)           |
| Perindopril          | 328 (15.9) | 1,353 (17.4) | 1.02 (0.75, 1.40)          |
| Ramipril             | 1651 (79.8) | 6,124 (78.8) | 1.10 (0.83, 1.45)          |
| All-cause mortality  | n = 1953 | n = 7234 | 1.00 (reference)           |
| Lisinopril           | 78 (4.0) | 228 (3.2) | 1.00 (reference)           |
| Perindopril          | 306 (15.7) | 1,394 (19.3) | 0.83 (0.59, 1.18)          |
| Ramipril             | 1569 (80.3) | 5,612 (77.6) | 0.97 (0.70, 1.34)          |

*Adjusted for age, income quintile, long term care residence, Charlson comorbidity score, hypertension, diabetes, stroke, peripheral vascular disease, chronic kidney disease, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft, cardiac dysrhythmia, angina, total number of drugs, amiodarone, calcium channel blockers, digoxin, insulin, loop diuretics, nitrates, oral glucose-lowering drugs, spironolactone, statins and warfarin.

**Discussion**

In this population-based study spanning over a decade, we found that among older individuals newly commencing clopidogrel following acute myocardial infarction, use of ramipril or perindopril (prodrug ACE inhibitors activated by CES1) was not associated with an increased risk of reinfarction, heart failure or death relative to lisinopril (an active ACE inhibitor). These findings suggest that the recently described drug interaction between clopidogrel and prodrug ACE inhibitors is of little clinical relevance.

CES1 is involved in the bio-activation of prodrug ACE inhibitors and is competitively inhibited by clopidogrel in vitro [19, 20]. A recent study by Kristensen and colleagues examined the potential clopidogrel–ACE inhibitor drug interaction and observed a modest increase in the risk of adverse cardiac events (acute myocardial infarction, cardiovascular death or stroke) in patients prescribed clopidogrel with an ACE inhibitor relative to those prescribed an ACE inhibitor alone (hazard ratio 1.12, 95% CI 1.06, 1.19) [23]. This finding may reflect baseline differences in the characteristics of patients treated with clopidogrel relative to those who are not. By restricting our analysis to older individuals with ongoing use of clopidogrel and an ACE inhibitor, we examined a relatively homogenous population, and minimized selection bias by limiting the analysis to patients receiving one of three commonly prescribed ACE inhibitors. We assert that if clopidogrel inhibits CES1 in a clinically meaningful way, this interaction may result in a modest increase in the risk of adverse cardiac events.
way, this would impair bioactivation of prodrug ACE inhibitors, attenuating their clinical benefit. If this were the case, patients taking clopidogrel with either ramipril or perindopril (prodrug ACE inhibitors activated by CES1) should be more prone to adverse cardiovascular events than patients taking clopidogrel with lisinopril (an active ACE inhibitor). We found no such differences, suggesting that this recently described interaction is unlikely to be of clinical relevance.

Although clopidogrel can clearly inhibit CES1 in vitro, there are several reasons why this observation may not be clinically relevant. First, clopidogrel concentrations used in drug inhibition studies (20–50 μM) are generally much higher than those achieved in vivo after a 75 mg oral dose (2.2–2.5 ng ml⁻¹) [19, 20]. Second, clopidogrel is highly protein bound (>98%) and unbound clopidogrel will constitute only a small fraction of total drug concentrations. This is important because unbound drug concentrations are a more important determinant of enzyme inhibition than total drug concentration in plasma [35]. Third, clopidogrel concentrations decline quickly from maximal concentrations ($t_{max}$=60 min, $t_{1/2}$=6 h), and any inhibition of ACE inhibitor metabolism may therefore be temporary.

Some limitations of our study warrant emphasis. Our conclusions derive from patients aged 66 years and older, and the generalizability of our findings to younger patients is unknown. Although we used validated outcome definitions with high sensitivity and specificity [25, 33], some degree of outcome misclassification is likely. Importantly however, this applies equally to all the ACE inhibitors we studied. We did not examine all available ACE inhibitors, choosing instead to focus on the agents most widely prescribed in Ontario, with the rationale that this would be sufficient to confirm or refute a clinically important drug interaction while minimizing unnecessary comparisons. Although we adjusted for several clinical covariates, we did not have information on non-prescription drug use and other important factors including smoking and other lifestyle factors, and the adequacy of control of hypertension, blood glucose or dyslipidaemia. Again, these limitations apply equally to ramipril, perindopril and lisinopril, although we may not have been able to adjust for any residual differences in these characteristics between exposure groups. Finally, there was some degree of imbalance between cases and controls due to the nature of design. This is expected, because cases are defined by the occurrence of an adverse outcome but controls are not. Regardless, the key comparison in our study is not between cases and controls, but rather between ACE inhibitor type (prodrug vs. active drug).

In conclusion, among older individuals commencing clopidogrel therapy following acute myocardial infarction, use of the prodrug ACE inhibitors ramipril or perindopril was not associated with an elevated risk of recurrent myocardial infarction, heart failure or death relative to use of lisinopril. These results offer a measure of reassurance that the recently described interaction between clopidogrel and prodrug ACE inhibitors is of little relevance to patients taking these medications concomitantly.

### Competing Interests and Financial Disclosure

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work. During the past 3 years, Muhammad M. Mamdani has been on advisory boards and/or received honoraria from Astra Zeneca, Bristol-Meyers Squibb, Eli Lilly and Company, Glaxo Smith Kline, Hoffman La Roche, Novartis, Novo Nordisk and Pfizer. None of the other authors have any conflicts of interest to disclose and there are no other relationships or activities that could appear to have influenced the submitted work.

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### Author Contributions

**Study concept and design:** AMC, EMM, KAF, TG, JMP, MMM, DNJ  
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All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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