PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study.
AUTHORS	Currie, Olivia; Mangin, Dee; Williman, Jonathan; McKinnon-Gee, Bianca; Bridgford, Paul

VERSION 1 - REVIEW

REVIEWER	Doron Garfinkel, M.D. Clnical Assistant Professor, Deputy head, Homecare Hospice, Israel Cancer Associaiton & consultant, Maccabi Healthcare Services, Israel. I have NO CONFLICT OF INTEREST
REVIEW RETURNED	29-Jul-2013

REPORTING & ETHICS	A very important research that warns again the possibility of accumulating late onset adverse events of medications prescribed for prevention. This in turn highlights a much broader problem – the somewhat compulsive way of modern, defensive medicine to prescribe a variety of preventive medication for unlimited periods of time, sometimes until death. RCTs on the effects of medications are usually performed by drug companies that can afford such expensive projects. Obviously, the whole study design may be biased and the endpoints chosen usually include mainly beneficial outcomes rather than adverse events that may or may not be published. The strength of this study stems from both the size of the sample and the apparently lack of such bias. Another important factor is that the endpoint measured is, in the authors' words: "an outcome that matters to patients", a point in patient's life when the diagnosis of diabetes mellitus is serious enough to require a specific medication for the disease.
GENERAL COMMENTS	The authors have to explain in more details the control group they entitle: "comparator drug". In the "results" section, subtitle "Primary analysis" lines 5-6 they write: " As known, patients on any cardiovascular risk modifying drugs had a higher risk of new-onset diabetes compared to patients receiving diclofenac"… This, in my view, should be moved to "Discussion" where the authors are supposed to clarify: "As known"... to whom? No reference? They should also explain in more details why they have chosen Diclofenac? Why not Paracetamol? or a commonly used antibiotic etc.). They have to discuss/suggest that patients who are on diclofenac (probably as a result of arthralgia or another pain related disorder), are not at risk of developing diabetes mellitus more than people of comparable demographic characteristics who are not on this medication.

REVIEWER	Beatrice A. Golomb, MD, PhD Professor of Medicine Professor of Family and Preventive Medicine University of California, San Diego
REVIEW RETURNED	09-Aug-2013

GENERAL COMMENTS	This is a good study overall, well written and presented, and a nice addition to the literature. The first use of a national population based cohort to assess incident diabetes rates associated with statin use (in patients receiving prescriptions for statins relative to other cardiovascular drugs (antihypertensives) and noncardiovascular drugs (diclofenac); examination in different ethnic groups) represents a particular strength. I think this should be viewed as complementing the findings from RCTs. While those are optimal for causal inference, they are poor for applicability to a real world setting. Via use of national prescribing data, these findings have exceptional value from the standpoint of relevance to an actually treated group. There are several relatively minor recommendations related to the text. 1. Verbiage in the abstract and elsewhere conveys the impression that there is need to support that a relationship between statins and new diabetes or increased glucose is causal, and not just due to those on statins having higher baseline risk. The conclusion of the abstract, as though this conclusion follows newly from these study data, states: "Not all the risk of diabetes associated with statins can be attributed to increased background risk." A different concluding sentence should be selected, since that conclusion clearly antedates this study. But the causal nature of the association is not in doubt, since randomized trials, which have high authority for causal inference (and involve people with the same metabolic risk in treated and placebo groups) have also shown diabetes increases, including JUPITER and PROVE-IT/TIMI, as well as several meta-analyses of randomized trials, have reported significant increases in incident diabetes and/or glycemia with statins relative to placebo. Verbiage suggesting that there is dispute regarding causality should be modified. (You might conclude with something like, these findings, using a different approach, further support the link between statin use and incident diabetes; and suggest the understanding of diabetes risk associated with antihypertensive drugs may bear revision/modification.) (Our own RCT also affirmed that glycemic rise occurs on statins relative to placebo and shows within a RCT that effect modification operates. Our findings for men in our sample showed that, even with low statin doses, and for both simvastatin and pravastatin, older age and presence of metabolic syndrome precursor factors (and greater number of such factors) predicted significantly increased glucose rise on statins vs placebo^1. I will include the abstract here between asterisks.) *** Here is an abstract that supports (in placebo-controlled fashion) the notion that pravastatin is not exempt from glucose concerns, in those vulnerable to glucose-elevating effects. In this RCT, simvastatin 20mg lowered LDL significantly more than did pravastatin 40mg (49 vs 40mg/dL ($p<0.001$) total sample; 48 vs 41 mg/dL ($p<0.01$), among men in the sample. http://circ.ahajournals.org/cgi/content/meeting_abstract/125/10_MeetingAbstracts/A055?sid=03c0b492-f7ab-4ee4-abf6-32a25a56abf7 *** (In looking up the citations, citation 8 does refer to JUPITER, and from this and other citations the authors appear to be aware of randomized trial evidence for diabetes risk on statins, in at least some settings; this should be better reflected, including in the beginning of the introduction. Your paper makes an excellent contribution, without implying it is the first causal evidence.)

	2. There is a Key Content-affecting wording/ transposition error that needs correction. The text notes that thiazide diuretics and beta blockers are most strongly associated with increased risk of diabetes ("Thiazide diuretics (T) and beta-blockers (BB) are most strongly associated with an increased risk,^14, 17-19"). The abstract notes that "followed by patients prescribed antihypertensives thought less likely to induce diabetes (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01) and patients prescribe antihypertensives thought more likely to induce diabetes (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) in the subsequent 6 years of follow up, when compared to diclofenac" – that is, the higher risk was present in those with the expected lower risk. This would mean that the 2.32 was associated with ACE inhibitors and CCBs; and the 1.59 with thiazides and beta blockers. However, the Key messages states: "Patients on antihypertensives are also likely to receive their first metformin prescription when prescribed thiazides and beta-blockers (HR: 2.32; 95% CI: 1.74 to 3.09; P < 0.01), and ACEi, ARB and CCB (HR: 1.59; 95% CI: 1.15 to 2.20; P < 0.01) compared to control drug. However, this risk is not as high as those on statins." These statements are mutually inconsistent. Compared to the results, it appears that it is the Key Messages that is in error, and should be corrected. 3. Additional sources of potential bias and confounding should be acknowledged in the discussion. It is stated that "These are major uncontrolled confounding and effect modifiers that cannot be accounted for in this study, however there is no indication to suggest that these risk factors would be unevenly distributed between the high risk prescription groups." First, although usage may perhaps differ, per graduate coursework in Epidemiology Methods at UCLA from Dr. Hal Morgenstern, who literally "wrote the book" on epidemiology methods (or at least coauthored a major text), a variable is a confounder if and only if it relates both to the exposure in the total base population, and to the outcome in the unexposed (and is not in the causal pathway); so to be a confounder, by definition it would be need to be unevenly distributed, since related (differentially) to the exposure. Second, this is not quite true, and for this reason I would leave off the "however…" portion and disclose the presence of some possible sources of confounding (which are virtually always present in observational studies). Risk of subsequent glucose elevation relates to the presence and number of metabolic syndrome factors, off as well as on statins, and statin use more than antihypertensive use takes into consideration several such factors, in guiding statin use at a given lipid level. (That is, the greater the number of such factors, the greater the likelihood that patients will surpass a risk threshold that will lead to statin use, at a given lipid level.) The fact that more such factors leads to greater risk of diabetes relative to fewer was put in strong relief in the abstract above; in that size sample over a mere 6 months this was significant only in the group on statins (and age >55), as that is where power was greatest, but the principle holds overall. I am not familiar with evidence directly examining whether diclofenac increases, reduces, or is neutral vis a vis diabetes risk. However, conceptually it could confer protection, as diclofenac is anti-inflammatory, and inflammation relates strongly to diabetes risk. The discussion might add reference to this potential source of bias. (In principle, this could lead the "baseline" comparator risk, on diclofenac, to be lowered relative to a hypothetical neutral level, leading to appearance of elevation in risk for those on cardiovascular drugs. However, the known relation to B+T antihypertensives provides relative assurance that this is not the full explanation.)

	I wondered if timing of prescribing could be a consideration. Are there people who might have been ascertained to have apparent diabetes and placed on a statin (because some prescribers consider diabetes to require more stringent lipid criteria), with a metformin prescription slightly lagging a trial of lifestyle for diabetes? Again, to the extent that timing might be unclear from medical records, this might bear addition to the discussion. Metformin use may fail to capture milder diabetes instances, as you note; but in some settings it may also fail to capture severe diabetes instances, if patients present initially with a diabetic urgency/emergency and are placed initially on other agents such as insulin (including following hospitalization). 4. A couple of Strobe items were not checked, those related to discussion of bias 9, study size 10, and missing data 12. 5. I would recommend deleting bullet c under strengths. I cannot completely speak for practice in New Zealand but first prescription of metformin in the US need not have bearing on whether lifestyle modifications could have played a role. You might just say, defined by first prescription of a common class of diabetes medication. 6. I thought the information on other ethnicities was interesting and potentially important. It is an issue I have long wondered about. I wouldn't mind seeing this played up a little more. 7. MINOR: Typos (which may alternatively be errors introduced in conversion to pdf). For instance: "at least one of the drug of interest between 2005 and 2011." (Should be drugs of interest.) The spelling of rosuvastatin (as rosuvostatin) in citation 8 (the Ridker JUPITER citation). There is an early "return" (key stroke) in the text: "after exposure compared to the Control group (HR: 3.31; 95% CI: 2.56-4.30; P < 0.01). In contrast to existing research, patients on Antihypertensives AAC" (There was at least one more but I am not recalling where.) Clarify meaning: "Antihypertensives AAC group have moderate risk of receiving their first prescription of metformin in 6 years (HR: 2.32; 95% CI: 1.74-3.09; P < 0.01), and patients in the Antihypertensives TB group had a slightly higher risk (HR: 1.59; 95% CI: 1.15-2.20; P < 0.01)" – Higher than who, than those on antihyperstensives AAC? Presumably no, so presumably you mean slightly elevated risk (since "higher" sounds comparative to the previously mentioned group). References 1. Golomb BA, Koperski S, White HL. Statins Raise Glucose Preferentially among Men who are Older and at Greater Metabolic Risk. Epidemiology and Prevention; Nutrition , Physical Activity and Metabolism 2012 Scientific Sessions. San Diego, CA, 2012.

VERSION 1 – AUTHOR RESPONSE

I am very much encouraged by the feedback you have provided. Your attention to the details of my work is much appreciated and I hope my response will be equally as thorough in return.
I have heeded to the advice and suggestions provided in your report and have made necessary changes to the original manuscript. I am unable to make the following changes but will explain my reasoning as below:
Prof. Golomb's comment #3
Your point on the timing of prescription is of consideration. Given the utility of electronic prescription data, this is difficult to ascertain as data are collected quarterly within the year. The guidelines for prescribing statins in New Zealand (ref 20) may also mean that only a minority of prescribers will adhere to that practice. Of course, this is only an assumption of how physicians practice in New Zealand as we have no access to medical records beyond the electronic prescription database. This comment, however, has provoked thoughts for my own clinical practice and will be considered for my future practice and research.
Prof. Golomb's comment #6
The findings of the ethnicity data were also interesting to us here. Again, due to the limitation of the electronic database and coding system, our analysis was limited only to what is available.

VERSION 2 – REVIEW

REVIEWER	Beatrice A. Golomb, MD, PhD Professor of Medicine Professor of Family and Preventative Medicine University of California, San Diego School of Medicine
REVIEW RETURNED	01-Oct-2013

GENERAL COMMENTS	This is a nice paper, and the prior comments have been well addressed. I have a few very minor points, mostly typo- or language related. There is one substantive point, 1, which I think has been addressed maybe more obliquely; but I view the paper as acceptable in its current state. 1. It is stated: "Presence of metabolic syndrome risk factors also increased the risk of subsequent glucose elevation, on as well as off statin use.^28 This study is not able to answer these questions, but raises these for future research." – This is an important point vis a vis interpreting this paper, since both dyslipidemia that may lead to statins, and hypertension that may lead to antihypertensives, are metabolic syndrome factors associated with increased risk of incident diabetes. (This means for both antihypertensives and statins, it may both be the case that the condition treated is a risk marker for increased risk (reflecting underlying processes); and also the case that correcting the factor with these medications may be a risk factor for increased risk (causal). (I have elsewhere reviewed why both are the case^1.) It might bear making a bit more explicit in the limitations that the conditions that lead to cholesterol drugs and antihypertensive drugs (i.e. dyslipidemia and hypertension) are tied to greater risk of glucose elevation (moreso low HDL and high triglycerides, in terms of lipids), so that some of the risk on both statins and antihypertensive drugs may arise (or indeed be expected to arise) from the risk associated with the condition the drugs treat; however, not all can be ascribed to this, given RCT support for glucose elevations with these drugs. (Randomization relatively protects

	against systematic differences in these factors.) My preference is to be up front about limitations, but your above sentence “Presence of metabolic syndrome risk factors…” does allude to this (if somewhat obliquely); I will leave this to the authors’ discretion. {FYI, relevant to the finding (but not necessary to cite), we have shown why it is the case that dyslipidemia and elevated BP are risk markers demonstrating underlying processes associated with risk of glucose elevation, while concurrently cholesterol reduction and blood pressure reduction are expected to statistically increase serum glucose (as energy adaptations)^1. We have also generated affirmative evidence, from an RCT setting, showing that glucose elevations on statins in older individuals serve as an energy adaption and protect against fatigue^2.} MINOR POINTS: 2. (Same sentence as above): “Presence of metabolic syndrome risk factors also increased the risk of subsequent glucose elevation, on as well as off statin use.^28 This study is not able to answer these questions, but raises these for future research.” – This last point is not framed as a question, so might adjust the wording. 3. Text in Limitations currently reads: “Confounding factors like BMI, family history and socioeconomic status is not controlled for in this electronic database analysis. However, there is no indication that these factors are not unevenly distributed between the different “high risk” study groups.” 4. Change “factors… is not controlled for” to “factors… are not controlled for”. 5. Change from “no indication that these factors are not unevenly distributed” – Change to “no indication that these factors are unevenly distributed” Reason: Double negative is a positive, suggests they are unevenly distributed. 6. Text under primary analysis: “(HR: 3.31; 95% CI: 2.56-4.30elevated” – Presumably there should be a space or a comma and space prior to the word “elevated”, if it is intended to be there at all? The loss of space may be an error occurring in the conversion to PDF document. 7. Text reads: “Secondly, it may be that patients with risk factors for diabetes (such as obesity) are less likely to be prescribed treatment with associated increased risk of diabetes.^14,27” – Suggest you might rewrite this sentence to be clearer. After a few readings and in the context, one can certainly infer what you mean, but on initial reading the interpretation is potentially ambiguous, and it never hurts to spare the reader the effort. (As it stands, it could be misread to mean that they are less likely to be prescribed treatment – and that this lesser likelihood may lead them to increased (“associated”) risk of diabetes. That is, people could mentally

	interpret the sentence in the way it would be interpreted with a comma after the word “treatment”.) 8. Text reads: “The effect seen carries an exposure duration response groups, and is also seen in patients prescribed relatively low doses of these drugs, which is important information for prescribers.” – Recommend rewriting the sentence for clarity. 9. In the following: “Diabetes, as a diagnosis based on a measurement, is itself a source of morbidity and mortality largely only as a risk factor for other disease, predominantly cardiovascular disease.” – Might consider eliminating the word “only” and just leave it at “largely”. I have practiced long enough that I can still recall many patients presenting for care initially with diabetic urgencies and emergencies, in which symptoms are present from the hyperglycemic state (polyuria, polydipsia, polyphagia, weight loss, DKA etc). Now of course it is commonly caught earlier before we see these, but that doesn’t mean they would not arise if given the chance… 10. Reference 28 can be updated to reference the Circulation abstract below (vs the meeting proceedings)^3. References Cited 1. Golomb BA. The starving cell: Metabolic syndrome as an adaptive process. Nature Precedings 2011; http://precedings.nature.com/documents/6535/version/1. 2. Golomb BA. Glucose Rise on Statins in Older Age: Adaptive Protection Against Fatigue? Circulation 2013;127:AP041. 3. Golomb BA, Koperski S, White HL. Statins Raise Glucose Preferentially among Men who are Older and at Greater Metabolic Risk. Circulation 2012;125:A055.

VERSION 2 – AUTHOR RESPONSE

I have heeded to your advice and suggestions, and have made necessary changes to the original manuscript.