

Cohort Study
Potential PURL Review Form
PURL Jam Version
Version #12 Sept 20, 2010

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Ou SM, Shih CJ, Chao PW, Chu H, Kuo SC, Lee YJ, Wang SJ, Yang CY, Lin CC, Chen TJ, Tarng DC, Li SY, Chen YT. Effects on Clinical Outcomes of Adding Dipeptidyl Peptidase-4 Inhibitors Versus Sulfonylureas to Metformin Therapy in Patients With Type 2 Diabetes Mellitus. Ann Intern Med. 2015 Nov 3;163(9):663-72. http://www.ncbi.nlm.nih.gov/pubmed/26457538
2. Hypertext link to PDF of full article	
3. First date published study available to readers	11/03/2015
4. PubMed ID	26457538
5. Nominated By	Other Other: Jennie Jarrett
6. Institutional Affiliation of Nominator	Other Other: UPMC St. Margaret's
7. Date Nominated	10/12/2015
8. Identified Through	Other Other: TOC
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland
10. Nomination Decision Date	11/02/2015
11. Potential PURL Review Form (PPRF) Type	Cohort Study
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Kate Rowland
14. Reviewer Affiliation	Other Other: Colorado
15. Date Review Due	12/03/2015
16. Abstract	BACKGROUND: Recent studies concluded that dipeptidyl peptidase-4 (DPP-4) inhibitors provide glycemic control but also raised concerns about the risk for heart failure in patients with type 2 diabetes mellitus (T2DM). However, large-scale studies of the effects on cardiovascular outcomes of adding DPP-4 inhibitors versus sulfonylureas to metformin therapy remain scarce. OBJECTIVE: To compare clinical outcomes of adding DPP-4 inhibitors versus sulfonylureas to metformin therapy in patients with T2DM. DESIGN: Nationwide study using Taiwan's National Health Insurance Research Database. SETTING: Taiwan. PATIENTS:

All patients with T2DM aged 20 years or older between 2009 and 2012. A total of 10 089 propensity score-matched pairs of DPP-4 inhibitor users and sulfonylurea users were examined.

MEASUREMENTS:

Cox models with exposure to sulfonylureas and DPP-4 inhibitors included as time-varying covariates were used to compare outcomes. The following outcomes were considered: all-cause mortality, major adverse cardiovascular events (MACEs) (including ischemic stroke and myocardial infarction), hospitalization for heart failure, and hypoglycemia. Patients were followed until death or 31 December 2013.

RESULTS:

DPP-4 inhibitors were associated with lower risks for all-cause death (hazard ratio [HR], 0.63 [95% CI, 0.55 to 0.72]), MACEs (HR, 0.68 [CI, 0.55 to 0.83]), ischemic stroke (HR, 0.64 [CI, 0.51 to 0.81]), and hypoglycemia (HR, 0.43 [CI, 0.33 to 0.56]) compared with sulfonylureas as add-on therapy to metformin but had no effect on risks for myocardial infarction and hospitalization for heart failure.

LIMITATION:

Observational study design.

CONCLUSION:

Compared with sulfonylureas, DPP-4 inhibitors were associated with lower risks for all-cause death, MACEs, ischemic stroke, and hypoglycemia when used as add-ons to metformin therapy.

17. Pending PURL
Review Date

**SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]**

1 The study addresses an appropriate and clearly focused question.

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed
- Not reported
- Not applicable

Comments:

2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed
- Not reported
- Not applicable

Comments:

3 The study indicates how many of the people asked to take part did so, in each of the groups being studied

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed
- Not reported
- Not applicable

Comments: retrospective cohort trial from a database review

4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed
- Not reported
- Not applicable

Comments: primary outcome included all-cause mortality, hospitalization for stroke, MI, HF, and hypoglycemia. Study identified comorbidities in each group

5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?

n/a

6 Comparison is made between full participants and those lost to follow up, by

- Well covered
- Adequately addressed
- Poorly addressed
- Not addressed
- Not reported
- Not applicable

Comments: Data review from registry; no follow up issues.

exposure status.

- 7** The outcomes are clearly defined.
- | | |
|--------------------------------------------------|-----------------------------------------|
| <input checked="" type="checkbox"/> Well covered | <input type="checkbox"/> Not addressed |
| <input type="checkbox"/> Adequately addressed | <input type="checkbox"/> Not reported |
| <input type="checkbox"/> Poorly addressed | <input type="checkbox"/> Not applicable |
- Comments:
- 8** The assessment of outcome is made blind to exposure status
- | | |
|-----------------------------------------------|---------------------------------------------------|
| <input type="checkbox"/> Well covered | <input checked="" type="checkbox"/> Not addressed |
| <input type="checkbox"/> Adequately addressed | <input type="checkbox"/> Not reported |
| <input type="checkbox"/> Poorly addressed | <input type="checkbox"/> Not applicable |
- Comments:
- 9** Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.
- | | |
|----------------------------------------------------------|-----------------------------------------|
| <input type="checkbox"/> Well covered | <input type="checkbox"/> Not addressed |
| <input checked="" type="checkbox"/> Adequately addressed | <input type="checkbox"/> Not reported |
| <input type="checkbox"/> Poorly addressed | <input type="checkbox"/> Not applicable |
- Comments:

- 10** What are the key findings of the study?
- After propensity score matching, follow-up was similar between groups (mean, 2.8 years [SD, 1.0 year])
- Users of DPP-4 inhibitors had lower risks for all-cause death (366 events vs 488; hazard ratio, [HR], 0.63 [95% CI, 0.55 to 0.72) and MACEs (209 events vs 282; HR, 0.68 [CI, 0.55 to 0.83]) than sulfonylurea users.
- DPP-4 inhibitor users also had lower risks for ischemic stroke (144 events vs 203; HR, 0.64 [CI, 0.51 to 0.81]) and hypoglycemia (89 events vs 170; HR, 0.43 [CI, 0.33 to 0.56]).
- However, risks for myocardial infarction (HR, 0.75 [CI, 0.52 to 1.07]) and hospitalization for heart failure (HR, 0.78 [CI, 0.57 to 1.06]) were similar between groups
- 11** How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests?
- no support from any funding agency in the public or commercial sector

SECTION 3: Review of Secondary Literature [to be completed by the Potential PURL Reviewer]

Citation Instructions For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online].

Available at: <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

1. DynaMed excerpts
DPP-4 inhibitors do not affect risk of cardiovascular events in patients with type 2 diabetes (level 1 [likely reliable] evidence) and may increase hospitalization for heart failure (level 2 [mid-level] evidence)

- glyburide and first-generation sulfonylureas may have dose-response relationship with mortality (level 2 [mid-level] evidence); tolbutamide may have increased risk for cardiovascular mortality (level 2 [mid-level] evidence)
- most common side effect is hypoglycemia; sulfonylureas may increase risk of severe hypoglycemia compared to metformin, thiazolidinediones, and possibly meglitinide but may have similar risk compared to insulin (level 2 [mid-level] evidence)
2. DynaMed citation/access date
Title. Glucose lowering medications for type 2 diabetes Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: Updated 2015 Oct 29 08:53:00 AM. Accessed
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
Each medication group may increase CV risk, but it is not clear.
4. UpToDate excerpts
The exact role for DPP-4 inhibitors among the myriad of other agents for management of type 2 diabetes is unclear. There are few long-term studies of DPP-4 inhibitors to assess glycemia-lowering efficacy, clinically important health outcomes (cardiovascular events, mortality), or safety. Many questions remain unanswered regarding clinical use in type 2 diabetes, including long-term benefits and risks and their role in combination with other diabetes medications.
The preliminary claims that DPP-4 inhibitors have a beneficial effect on cardiovascular disease (CVD) risk have not been borne out by the studies to date, although there does not appear to be an increased risk of adverse cardiovascular outcomes with short-term use of DPP-4 inhibitors used in combination with another oral agent.

Some studies suggest that sulfonylureas may be associated with poorer outcomes after a myocardial infarction.
Since most studies have compared cardiovascular events in sulfonylurea-treated patients with those in metformin-treated patients, it is uncertain whether the increase in relative risk for cardiovascular disease is owing to toxicity associated with sulfonylureas or protective effects of metformin.
Newer sulfonylureas, such as glimepiride, are selective for the pancreatic sulfonylurea receptors over the cardiac receptors and do not appear to be associated with increased cardiovascular mortality compared with metformin or other diabetes medications, although direct controlled clinical trials have not been performed
5. UpToDate citation/access date
Always use Basow DS as editor & current year as publication year.
Title. Sulfonylureas and meglitinides in the treatment of diabetes mellitus and (Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus) Author. David K McCulloch, MD and (Kathleen Dungan, MD Anthony DeSantis, MD)
In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: Sep 09, 2015 and (Nov 12, 2015).. Accessed 11/24/15
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
It is not clear what the risk for mortality and CVD is with either class
7. PEPID PCP excerpts

www.pepidonline.com

username: fpinauthor

pw: pepidpcp

8. PEPID

citation/access data

Author. Title. In: PEPID [database online]. Available at:

<http://www.pepidonline.com>. Last updated: . Accessed

9. PEPID content

updating

1. Do you recommend that PEPID get updated on this topic?

Yes, there is important evidence or recommendations that are missing

No, this topic is current, accurate and up to date.

If yes, which PEPID Topic, Title(s):

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (E) that should be updated on the basis of the review?

Yes, there is important evidence or recommendations that are missing

No, this topic is current, accurate and up to date.

If yes, which Evidence Based Inquiry (HelpDesk Answer or Clinical Inquiry), Title(s):

10. Other excerpts

(USPSTF; other guidelines; etc.)

11. Citations for other

excerpts

12. Bottom line

recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions

[to be completed by the Potential PURL Reviewer; Revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7

(1=extremely well; 4=neutral; 7=extremely poorly)

1 2 3 4 5 6 7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

They measured what they said they would measure

Observational design may decrease the validity slightly, but the use of propensity scoring helps

Noted they included 1st generation of sulfonylureas which are known to cause more side effects - unsure of how many of the patients used this generation of meds

Slight concern of Taiwan population compared to US population

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?

Give one number on a scale of 1 to 7

(1=extremely well; 4=neutral; 7=extremely poorly)

1 2 3 4 5 6 7

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.

Used POEMs of all cause mortality and cardiovascular events

May lose some relevance with Taiwan population and older generation of sulfonylureas

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these

Give one number on a scale of 1 to 7

(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)

1 2 3 4 5 6 7

findings represent a change from current practice?

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

7. Applicability to a Family

Medical Care Setting:

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain. .

9. Immediacy of Implementation:

Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient oriented outcomes:

Are the outcomes measured in the study clinically meaningful or patient oriented?

12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.

13. In your opinion, is this a Pending PURL?

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation

Probably. Sulfonylureas have traditionally been the 2nd line agent, and this would support using DPP-4s. Glucose control and morbidity data from complications from diabetes is lacking.

These meds are becoming generic, more affordable; unsure if this change is already happening

Give one number on a scale of 1 to 7

(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)

1 2 3 4 5 6 7

Give one number on a scale of 1 to 7

(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)

1 2 3 4 5 6 7

Insurance coverage could be a barrier to the DPP-4s

Give one number on a scale of 1 to 7

(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

1 2 3 4 5 6 7

all cause mortality and adverse cardiovascular events are POEMs. Missing is data on complications from diabetes.

Give one number on a scale of 1 to 7

(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)

1 2 3 4 5 6 7

that is applicable to what family physicians do in medical care settings and seems different than current practice.

- Applicability in medical setting:
- Immediacy of implementation

14. Comments on your response in 4.13

This could be. The observational design limits the strength of the evidence and we are unsure of any unmeasured confounders. However, the mortality and MACE outcomes, plus less hypoglycemia episodes would support using DPP-4s over sulfonylureas.

This article could assist in shared decision making

SI concern with study design - would this be overturned by an RCT?

This would help move away from sulfonylureas as the second line and by changing to DPP-4s, will not cause any additional harm, and may be better.

SECTION 4.1: Diving for PURLs

[optional for the potential PURL reviewer -if you wish to be the author on the summary]

1. Study Summary- Please summarize the study in 5-7 sentences

2. Criteria- note yes or no for those which this study meets

RELEVANT -
VALID -
CHANGE IN PRACTICE-
MEDICAL CARE SETTING -
IMMEDIATELY APPLICABLE -
CLINICALLY MEANINGFUL -

3. Bottom Line- one –two sentences noting the bottom line recommendation

4. Title Proposal

SECTION 5: Editorial Decisions

[to be completed by the FPIN PURLs Editor or Deputy Editor]

1. FPIN PURLs editorial decision (select one)

- 1 Pending PURL Review—Schedule for Review
- 2 Drop
- 3 Pending PURL

3. Follow up issues for Pending PURL Reviewer

3. FPIN PURLS Editor making decision

- 1 Bernard Ewigman
- 2 John Hickner
- 3 Sarah-Anne Schumann
- 4 Kate Rowland

4. Date of decision

5. Brief summary of decision

SECTION 6: Survey Questions for SERMO, PURLs Instant Polls and Other Surveys

[To be completed by the PURLs Survey Coordinator and PURLs Editor]

1. Current Practice Question for Surveys
2. Barriers to Implementation Question for Surveys
3. Likelihood of Change Question for Surveys
4. Other Questions for Surveys

SECTION 7: Variables for Secondary Database Analyses

1. Population: Age, gender, race, ethnicity
2. Diagnoses
3. Drugs or procedures

SECTION 8: Pending PURL Review Assignment [to be completed by PURLs Project Manager]

1. Person Assigned for Pending PURL Review
2. Date Pending PURL Review is due

SECTION 9: Pending PURL Review [to be completed by the Pending PURL Reviewer]

1. Did you address the follow up issues identified at the PURL Jam (Section 5.2). Add comments as needed.
 Yes
 No
 Not applicable
Comments:
2. Did you review the Sermo poll & Instant Poll results (if available)? Add comments as needed.
 Yes
 No
 Not applicable
Comments:
3. Did you modify Sections 2, 3, or 4? Add comments as needed.
 Yes
 No
 Not applicable
Comments:

SECTION 10: PURL Authoring Template
[to be completed by the assigned PURL Author]

Author Citation Information (Name, Degrees, Affiliation)

1. Practice Changer

2. Illustrative Case

3. Background/
Clinical Context/Introduction/Current Practice/

4. Study Summary

5. What's New

6. Caveats

7. Challenges to Implementation

8. Acknowledgment Sentence

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If using UHC data:

We acknowledge Sofia Medvedev of University HealthSystem Consortium (UHC) in Oak Brook, IL for analysis of the National Ambulatory Medical Care Survey data.

9. References