Editorial European Urology

REPURPOSING METFORMIN AS THERAPY FOR PROSTATE CANCER WITHIN THE STAMPEDE TRIAL PLATFORM

Version 6
20-Jun-2016

[1]Silke Gillessen

[2]Clare Gilson

[3]Nick James

[5]Amanda Adler

[2]Matthew R Sydes

[4]Noel Clarke

On behalf of the STAMPEDE Trial Management Group (TMG)*

[1] Department of Oncology/Haematology, Kantonsspital, St. Gallen, Switzerland

[2] MRC Clinical Trials Unit at UCL, London, UK

[3] Warwick Medical School, University of Warwick, Coventry, UK; University Hospitals Birmingham NHS Foundation Trust, The Medical School, University of Birmingham, Birmingham, UK

[4] Department of Urology, The Christie and Salford Royal NHS Foundation Trusts, Manchester, UK

[5] Diabetes Service, Addenbrooke's Hospital, Cambridge, UK

*****The TMG:
Clinical members: Nick James, Gerhardt Attard, Noel Clarke, Bill Cross, David Dearnaley, Silke Gillessen, Clare Gilson, Rob Jones, Malcolm Mason, Chris Parker, Alastair Ritchie, Martin Russell, George Thalmann.
Statistical members: Mahesh Parmar, Melissa Spears, Matthew Sydes.
Patient members: Robin Millman, David Matheson.
Trial and Data Management Members: Claire Amos, Nargis Begum, Clare Gilson, Claire, Murphy, Orla Prendiville, Francesca Schiavone, Melissa Spears, Matthew Sydes, Carly Au, Peter Vaughan, Zohrah Khan, Estelle Cassoly

STAMPEDE is registered on ClinicalTrials.gov as NCT00268476

1. Rationale for evaluating metformin

The current standard-of-care (SOC) for men presenting with high-risk locally advanced or metastatic prostate cancer (CaP) includes long-term androgen deprivation therapy (ADT), a treatment associated with metabolic dysfunction, including insulin resistance, hyperglycaemia and obesity. Over 50% who receive long-term ADT develop a form of metabolic syndrome, thus potentially increasing their risk of cardiovascular morbidity and mortality.(1) The median overall survival for this patient population is now almost 6 years The need to mitigate the debilitating effects of prolonged ADT is increasingly relevant.

Metformin has proven benefit in that setting. In non-diabetics the incidence of diabetes is lowered and adverse metabolic effects of ADT, including hyperinsulinaemia and dyslipidaemia are reduced.(2) In diabetics, metformin decreases myocardial infarction risk and prolongs survival.(3)

These effects may be explained by the activation of Adenosine Monophosphate Activated Kinase (AMPK) which inhibits fatty acid synthesis, reducing levels of cholesterol, LDLs and triglycerides. Metformin also decreases platelet-aggregation factor 1, other vascular adhesion molecules and CRP.(4, 5) Metformin has anti-neoplastic properties, possibly explained by pre-clinical data showing that cancer progression is linked integrally with metabolic modulators.(6) Modification of this process by metformin has the potential to impact on prostate-cancer specific survival.(7, 8)

Metformin reduces hyperinsulinaemia, which promotes cancer metastasis, growth, and treatment resistance.(9) In prostate cancer models, insulin increases mRNA and protein expression of steroidogenic enzymes, up-regulating intracellular testosterone levels and androgen receptor (AR) activation.(10) By reducing hyperinsulinaemia, metformin can influence multiple other cancer pathways including insulin-like growth factor (IGF) and PI3K-AKT / AR signalling, both of which are associated with prostate cancer progression and castrate resistance. Metformin also exerts an anti-proliferative effect via the inhibition of mTOR and may target cancer stem cells and also epithelial to mesenchymal transition, thereby inhibiting metastatic progression (12).

Cancer outcomes in diabetic men receiving metformin provide epidemiological evidence of anti-cancer effect. A meta-analysis of 9,186 men with diabetes and CaP, showed metformin decreased biochemical recurrence and improved overall survival.(13)

In response to supporting pre-clinical, clinical and epidemiological evidence of anti-cancer effect, trials are now evaluating metformin in lung, breast, pancreatic and ovarian cancer. Encouraging non-randomised phase II data in castrate resistant CaP demonstrated 36% of patients treated with metformin were progression free at 3 months. When compared with baseline values, the PSA doubling time was prolonged in 52%, and overall clinical benefit was observed in 46%.(14, 15). Ongoing trials in CaP include the Metformin Active Surveillance Trial (MAST), recruiting men with low-risk CaP (NCT01864096) and trials adding metformin to abiraterone or docetaxel in the castrate resistant setting (NCT01796028, NCT01677897). To our knowledge, there are no ongoing or planned trials that will evaluate metformin in men with high-risk locally-advanced or metastatic CaP newly commencing long-term ADT.

2. Evaluating metformin in the STAMPEDE trial

The ongoing STAMPEDE trial evaluates whether adding therapies to the SOC improves survival in men with high-risk localised or metastatic (M1) CaP. By Jun-2016, more than 8,000 consenting men at >100 centres in the UK and Switzerland had joined the trial platform which, through using a multi-arm, multi-stage (MAMS) design, will undertake 9 randomised comparisons.(**Figure 1**) STAMPEDE is in a unique position to address two new and important questions: can the anti-diabetic drug metformin be repurposed to mitigate ADT related metabolic dysfunction and can it improve survival in CaP patients?

The “metformin comparison” will compare SOC plus metformin (new research arm K) to the current SOC (control arm A). For inclusion men must be non-diabetic (HbA1c<6.5%, equivalent to <48mmol/ml) and meet a more stringent renal cut-off than currently used in the trial (Creatinine clearance >60mls/min). Allocation will be 1:1, to control or research arm K. Currently, eligible newly-diagnosed M1 patients can also be allocated to receive prostate RT (arm H). Future MAMS trial principles for the metformin comparison are different from hitherto: overall survival will be used as both the intermediate and definitive primary outcome measure. Failure-free survival (used in other comparisons as the intermediate primary outcome measure) is driven predominantly by PSA failure and therefore was judged not to be appropriate in determining metformin benefit. The drug will be continued throughout long-term ADT and past the FFS event. Approximately 1800 patients will be required (included approximately 1200 metastatic patients) to achieve 85% power to detect a

20% relative improvement in overall survival at the final efficacy stage. Metabolic parameters evaluated will include BMI, HbA1c, fasting glucose and lipid profile and any new manifestation of cardiovascular disease or diabetes mellitus.

3. Challenges and considerations

:: Tolerability

Metformin is well-tolerated and ongoing trials evaluating its use in non-diabetic men report discontinuation rates due to toxicity to be low (~4%). Lactic acidosis, the most serious toxicity, is very rare and may be due to underlying diabetes and not metformin treatment. This is supported by a meta-analysis demonstrating comparable rates of lactic acidosis in untreated diabetic patients compared to those treated with metformin.(16)

:: Optimal duration of treatment

Metformin can be safety added to other treatments currently used in CaP and, as several of these involve co-prescribed steroids, addition of metformin may help counteract the steroid-induced hyperglycaemia. Metformin will be continued alongside long-term ADT and given in addition to all subsequent treatments. Men with M0 disease at trial entry will receive metformin for 3 years after randomisation or until 12 months after the last administration of a LHRH analogue, whichever is longer. Men with M1 disease will have life-long therapy provided it is tolerated and safe. The long-term duration of metformin administration for anti-cancer testing is guided by epidemiological evidence showing that it reduces the risk of CaP progression when it is given for 3 or more years.(17)

:: Feasibility

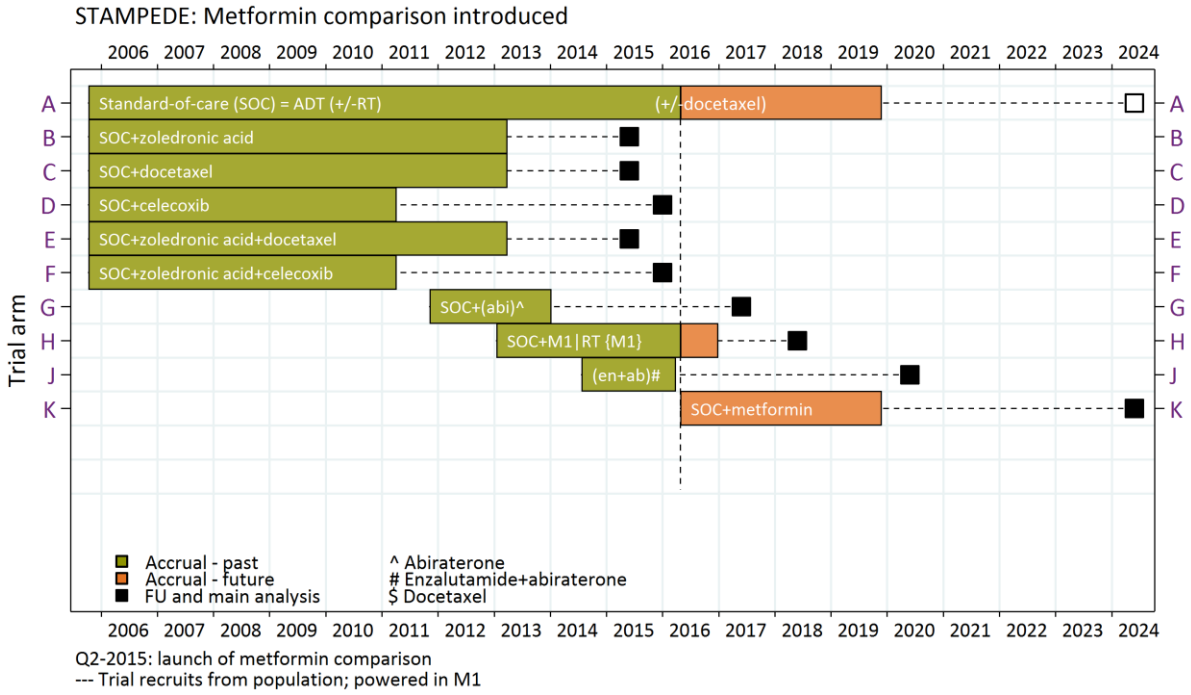
As a generic, low-cost drug, if shown to be beneficial, metformin could have an impact in both high- and low-resource health systems. Taken together with its low-toxicity profile, this means a smaller relative improvement is likely to be clinically significant. However, the absence of industry support means the acquisition of data is dependent on academic-led studies, which are required to be large in order to have the sufficient power to detect a smaller difference. Trial platforms such as STAMPEDE which evaluate multiple therapeutic approaches can attract both industry and charitable support and accrue at a sufficient rate necessary to address these globally important questions in a feasible timescale.

4. Conclusions

Metformin is a safe, well-tolerated, inexpensive treatment that can be given in addition to the current SOC therapies for CaP. Its use might mitigate the deleterious side-effects of castration and also exert an additional anti-cancer effect. It is under investigation in multiple tumour types and with the support of the investigators, patients and funders (Cancer Research UK and the UK Medical Research Council) it will be incorporated into the STAMPEDE trial platform in summer 2016. This will test its true utility as a re-purposed treatment for men with high-risk locally advanced or metastatic CaP at first presentation.

1139 words (including headings)
17 references

Figure 1: STAMPEDE accrual activity over time



REFERENCES

1. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. The Journal of clinical endocrinology and metabolism. 2002 Feb;87(2):599-603. PubMed PMID: 11836291.

2. Eriksson A, Attvall S, Bonnier M, Eriksson JW, Rosander B, Karlsson FA. Short-term effects of metformin in type 2 diabetes. Diabetes, obesity & metabolism. 2007 Jul;9(4):483-9. PubMed PMID: 17587390.

3. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. PubMed PMID: 9742977.

4. Ohira M, Miyashita Y, Ebisuno M, Saiki A, Endo K, Koide N, et al. Effect of metformin on serum lipoprotein lipase mass levels and LDL particle size in type 2 diabetes mellitus patients. Diabetes research and clinical practice. 2007 Oct;78(1):34-41. PubMed PMID: 17374417.

5. Wulffele MG, Kooy A, de Zeeuw D, Stehouwer CD, Gansevoort RT. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. Journal of internal medicine. 2004 Jul;256(1):1-14. PubMed PMID: 15189360.

6. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. Journal of the National Cancer Institute. 2009 Jan 7;101(1):48-60. PubMed PMID: 19116382. Pubmed Central PMCID: PMC2639294.

7. Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013 Sep 1;31(25):3069-75. PubMed PMID: 23918942.

8. Raval AD, Thakker D, Vyas A, Salkini M, Madhavan S, Sambamoorthi U. Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2015 Jun;18(2):110-21. PubMed PMID: 25667109.

9. Garland J. Energy management - a critical role in cancer induction? Critical reviews in oncology/hematology. 2013 Oct;88(1):198-217. PubMed PMID: 23731619.

10. Lubik AA, Gunter JH, Hendy SC, Locke JA, Adomat HH, Thompson V, et al. Insulin increases de novo steroidogenesis in prostate cancer cells. Cancer Res. 2011 Sep 1;71(17):5754-64. PubMed PMID: 21747118.

11. Xu Y, Chen SY, Ross KN, Balk SP. Androgens induce prostate cancer cell proliferation through mammalian target of rapamycin activation and post-transcriptional increases in cyclin D proteins. Cancer research. 2006 Aug 1;66(15):7783-92. PubMed PMID: 16885382.

12. Rattan R, Ali Fehmi R, Munkarah A. Metformin: an emerging new therapeutic option for targeting cancer stem cells and metastasis. Journal of oncology. 2012;2012:928127. PubMed PMID: 22701483. Pubmed Central PMCID: 3373168.

13. Stopsack KH, Ziehr DR, Rider JR, Giovannucci EL. Metformin and prostate cancer mortality: a meta-analysis. Cancer causes & control : CCC. 2016 Jan;27(1):105-13. PubMed PMID: 26537119.

14. Rothermundt C, Hayoz S, Templeton AJ, Winterhalder R, Strebel RT, Bartschi D, et al. Metformin in chemotherapy-naive castration-resistant prostate cancer: a multicenter phase 2 trial (SAKK 08/09). Eur Urol. 2014 Sep;66(3):468-74. PubMed PMID: 24412228.

15. Hamilton RJ. Metformin for castrate-resistant prostate cancer: learning more about an old dog's new tricks. Eur Urol. 2014 Sep;66(3):475-7; discussion 7-8. PubMed PMID: 24472709.

16. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. Archives of internal medicine. 2003 Nov 24;163(21):2594-602. PubMed PMID: 14638559.

17. Preston MA, Riis AH, Ehrenstein V, Breau RH, Batista JL, Olumi AF, et al. Metformin use and prostate cancer risk. Eur Urol. 2014 Dec;66(6):1012-20. PubMed PMID: 24857538.