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## A renaissance for cardio-metabolic surgery: Better outcomes and lower costs?

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**A renaissance for cardio-metabolic surgery: Better outcomes and lower costs?**

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3 **A renaissance for cardio-metabolic surgery:**  
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3 Not too long ago surgeons routinely treated metabolic problems including  
4 hypertension, hyperlipidaemia and obesity. However, these areas declined as drug therapies  
5 became available and surgical approaches lost favour due to high rates of perceived  
6 complications. Surgery survived in specialist metabolic oncological applications for treatment  
7 of endocrine adenomas or carcinomas. Metabolic endocrine surgery has grown ever more  
8 sophisticated with better imaging, more sensitive sampling techniques, intra-operative  
9 endocrine monitoring using point-of-care assay technologies and the increasing use of  
10 minimal access and eventually robotic surgery techniques[1-3]. The diagnosis of primary  
11 hyperparathyroidism (PHPT) is more frequently made at a significantly earlier stage than in  
12 the past. Surgery is performed for both prognostic benefit and symptom relief. Surgical  
13 approaches have evolved rapidly in recent years with an evolution in minimally invasive  
14 procedures aided by improvements in preoperative localisation[4]. Day surgery procedures  
15 are common and intra-operative assays of parathyroid hormone can be used to confirm  
16 surgical success in minutes. Type II calcimimetic drugs that enhance the sensitivity of the  
17 calcium sensing receptor to calcium resulting in a decrease in PTH secretion are used in  
18 secondary hyperparathyroidism reducing the need for surgery in some patients[5], and may  
19 also have a selective role in complicated patients with PHPT and malignancy. In other areas  
20 surgery disappeared such as when initially H2 antagonists and later proton pump inhibitors  
21 (PPIs) replaced the need for gastric acid reduction by vagotomy.

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48 However, some patients with metabolic problems have remained refractory to  
49 treatment despite the increased availability of medical management strategies in primary care  
50 which are adequate for the vast majority of cases. Two fields where the focus of secondary  
51 and tertiary care centres is increasingly on refractory disease are hypertension and  
52 hyperlipidaemia while in obesity and type 2 diabetes medical therapies are either inadequate  
53 or could be considered barely adequate to control disease progression in an increasing number  
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3 of patients. Recently there has been the start of a renaissance of surgical approaches to the  
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5 management of these metabolic problems.  
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## 8 **Obesity**

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12 Obesity is a fast increasing problem in the Western and developing worlds. As  
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14 adiposity in the general population has increased the prevalence of morbid obesity  
15  
16 (BMI>40kg/m<sup>2</sup>) in the UK has risen from 1.5% (2000) to 2.4% (2009)[6, 7]. Lifestyle therapy  
17  
18 is recommended for all patients and some patients with moderate obesity (BMI 27-35 kg/m<sup>2</sup>)  
19  
20 receive additional weight-loss medications. However, the management of the morbidly obese  
21  
22 has remained problematic. Many of these patients potentially qualify for bariatric surgery  
23  
24 based on the NICE guidelines with qualifying criteria ranging depending on co-morbidities  
25  
26 from BMI 35 to 50kg/m<sup>2</sup> and with BMI >50kg/m<sup>2</sup> surgery is the preferred treatment  
27  
28 option[8]. The most severe group in medical terms are those patients with established  
29  
30 complications of obesity including diabetes and the sleep apnoea syndromes[9]. Classical  
31  
32 diet approaches have proved inadequate in morbidly obese patients[10] who have invariably  
33  
34 tried multiple diets. Orlistat, though often poorly tolerated, delivers a 3% average reduction in  
35  
36 weight in moderately obese patients [11] and has evidence for a 37% reduction in progression  
37  
38 to type 2 diabetes in compliant patients who achieved a net 4.8 kg weight loss[12]. Both  
39  
40 sibutramine and rimonabant delivered more weight reduction when they were still available  
41  
42 but were withdrawn due to side-effects[11]. Attempts are made to market novel compounds  
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44 with a primary indication for diabetes on the basis of their weight loss properties but most are  
45  
46 minimally more effective than metformin which delivers an average 2kg (2%) weight  
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48 reduction. The hyperbole associated with higher doses of liraglutide failed to note that it  
49  
50 delivered an average glycaemic response for a hypo-glycaemic drug (1.0-1.2% HbA<sub>1c</sub>) and  
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52 only a 1.8-5.5 kg (2-5%) weight loss[13, 14].  
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3 Upper gastrointestinal surgeons have revived and modified many of their techniques  
4 to deal with obesity. Laparoscopic gastric banding, banded gastroplasty and gastric bypass are  
5 now frequently performed for weight reduction even in day surgery and have a developed a  
6 formidable evidence base. The Swedish Obesity Surgery registry has shown that  
7 complications rates are low (<2%), long-term mortality is acceptable for such a high-risk  
8 group (2%) and patients lose 20-40% of weight depending on the procedure [15, 16]. Series  
9 of laparoscopic surgery show acute deaths in only 0.23%[17]. Gastric bypass surgery is  
10 associated with reductions in glycaemia to the extent that 75% are restored to  
11 'normoglycaemia' especially if the diabetes was of recent onset (<5years), 50% of cases of  
12 hypertension and sleep apnoea resolve and there is dramatic reduction in orthopaedic  
13 complaints allowing further surgery to occur if necessary[18]. After 7 years CHD mortality is  
14 reduced by 56%, diabetes mortality by 92% and cancer mortality by 60%. While the  
15 endocrinology of gastric bypass surgery has been partially clarified the mechanism by which  
16 gastric banding/gastroplasty works remains obscure. Though many anti-obesity drugs have  
17 been developed few have been either highly effective or safe[19]. Both implanted gastric  
18 stimulators to mimic the stretch reflex[20] and ghrelin agonists (e.g. MK-677 to reduce  
19 visceral adiposity)[21] and ghrelin binders in mice (Speigelmers)[22] have failed to duplicate  
20 the effect of surgery. In diabetes units the clinical problem is that many patients would benefit  
21 from operative intervention when assessed using health economic methods ( $BMI > 30 \text{kg/m}^2$ )  
22 yet the capacity of the system to provide the bed space and finance is exceeded. Thus, many  
23 health systems ration access to bariatric surgery by limiting its availability to higher risk  
24 groups.

## 56 Hypertension

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3 Refractory hypertension is another common problem[23]. Some is caused by non-  
4 compliance with increasingly complex regimes, or due to the side-effects of non-specific  
5 vasodilation resulting in episodes of hypotension especially in patients with isolated systolic  
6 hypertension who have decreased vascular compliance. Many cases though are multi-factorial  
7 and associated with increasing age, obesity, renal dysfunction and left ventricular hypertrophy  
8 [23]. In the ALLHAT trial 27% of patients were not controlled despite triple therapy. This is  
9 not surprising as most anti-hypertensives deliver approximately a 10/5mmHg (6%) reduction.  
10 Many novel anti-hypertensives which seemed more effective in phase 3 studies have not  
11 reached clinical service. Angiotensin I-converting enzyme-neutral endopeptidase (ACE-  
12 I/NEP-I) inhibitors such as omapatrilat or samapatrilat delivered a 20/8mmHg (15%)  
13 reduction[24] but caused angioedema and were discontinued. The endothelin-I antagonist  
14 darusentan (LU-135252; HMR-4005) which remains in development reduced blood pressure  
15 by an added 18/11mmHg (11%) at a 300mg dose in patients with refractory hypertension in  
16 the DORADO study but was associated with high rates (30%) of peripheral oedema [25].  
17 More recently, a combined angiotensin-II receptor neprilysin antagonist (LCZ-696) was  
18 shown to reduce blood pressure significantly (5/3mmHg) more than the angiotensin-II  
19 receptor blocker (ARB) valsartan [26]. Given the importance of the renin-angiotensin system  
20 in the prognosis of heart failure the 400mg dose is now being investigated in the  
21 PARADIGM-HF trial in 8940 patients[27].  
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49 Surgery, and recently percutaneous radiofrequency ablation[28, 29], is still used for  
50 the treatment of secondary hypertension caused by localised aldosterone or noradrenaline  
51 (norepinephrine) secreting tumours but it is increasingly recognised that most patients with  
52 aldosterone-driven hypertension actually show generalised adrenal cortical hypertrophy  
53 where surgery is inappropriate. Medical therapy with spironolactone, eplerenone or amiloride  
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3 is used for cortical hypertrophy. It has been known for many years from animal studies that  
4 neuronal adrenal/renal stimulation results in an increase in blood pressure. De-nervation  
5 surgery for hypertension was used prior to the invention of anti-hypertensive drugs[30]. In a  
6 series of 1266 patients which included 226 with end-organ damage and diastolic BP  
7 >140mmHg splanchnicectomy as opposed to sedation reduced 5-year mortality by 31% but  
8 sub-group blood pressure data was not provided[31]. Modern data was lacking until the  
9 recent SYMPLICITY-2 HTN study of 106 patients with refractory hypertension (systolic  
10 blood pressure >160mmHg; average 178/98mmHg) was conducted. In these patients most  
11 secondary causes had been excluded and they were on >3 anti-hypertensive drugs so meeting  
12 the definition of refractory hypertension. Percutaneous radiofrequency renal de-nervation  
13 resulted in a 32/12mmHg (20%) reduction in blood pressure at 6 months [32]. The hyperbole  
14 following this single small surgical trial will tempt many to attempt surgery for hypertension  
15 but given past history, it remains to be seen which patients will benefit most from this  
16 intervention[33]. It may only be a sub-group and if that is the case then clinical pathways  
17 have to be devised to optimally define the target group for future surgery. Similar concerns  
18 may also be relevant to a surgically implanted carotid bulb baroreceptor stimulator (Rheos)  
19 system which reduced blood pressure by 22/12mmHg in 45 patients with resistant grade 2  
20 hypertension (179/105mmHg on 5 drugs) [34]. In this trial 17 patients achieved a  
21 33/22mmHg reduction at 2 years and the device is now in phase 3 trials[35].  
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### 49 **Hyperlipidaemia**

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52 Many think that hyperlipidaemia is treated solely by drug therapy. One common  
53 presentation to secondary care clinics is refractory hyperlipidaemia caused by side-effects to  
54 currently available therapies e.g. statins. Apheresis (dialysis/column extraction of  
55 lipoproteins) is effective in homozygous FH as patients are already secreting very low  
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3 density lipoprotein (VLDL) at a maximal rate and many also show a limited response to statin  
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5 therapy [36]. Apheresis has evidence from surrogate outcomes in homozygous FH. However,  
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7 patients with heterozygous FH are poorer candidates for apheresis as their potential for  
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9 increased rebound cholesterol synthesis is substantial. Though apheresis remains an option fo  
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11 for the treatment of these individuals it relies on drug therapy to reduce the rate of rebound of  
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13 LDL-C in the 2 week period between treatments so therapeutic options for drug-intolerant  
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15 patients are very limited. Yet another option does exist and does have an evidence base.

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21 Surgery was a potential option for treatment for hyperlipidaemia only 20 years ago. It  
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23 is still used in homozygous familial hypercholesterolaemia (FH) where liver transplantation to  
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25 restore hepatic LDL receptor function and particle clearance is common [37]. Some centres  
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27 used to use a portocaval shunt to reduce triglyceride and cholesterol flux to the liver and re-  
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29 secretion of these in very low density lipoproteins (VLDL) and therefore eventually as low  
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31 density lipoprotein (LDL)[38, 39].

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36 Homozygous FH is an ultra-orphan disease (prevalence  $<1$  in  $10^6$ ) but surgery used to  
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38 have indications in far less severely affected patients including those with heterozygous  
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40 familial hypercholesterolaemia or severe polygenic disease. Ileal bypass surgery reduces  
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42 LDL-C by a respectable 38%. The 834 patients in the Program on Surgical Correction of  
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44 Hyperlipidemia (POSCH) study randomised to surgery or medical management showed a  
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46 35% reduction in coronary heart disease (CHD) events after 7 years [40]. In post-trial  
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48 analyses this benefit continued and was associated with a 20% reduction in CHD mortality at  
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50 15 years [41] and further life benefit at 25 years[42]. These data are impressive as the surgery  
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52 conducted at the time was open resulting in significant extra morbidity compared to modern  
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54 minimally invasive techniques. An increase in events would be expected due to this and it is  
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56 notable that in POSCH the time to survival curve divergence is 3 years. No studies have  
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3 examined the potential effectiveness of laparoscopic ileal bypass surgery in  
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5 hypercholesterolaemia as opposed to diabetes and the metabolic syndrome [43, 44]. This  
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7 procedure should deliver equivalent LDL-C reductions with a far lower inflammation burden  
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9 and thus a quicker time to significant CHD event reduction. Randomised trials are difficult in  
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11 this field but a prospective randomised open blinded endpoint (PROBE) design might be  
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13 feasible.  
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18 The higher profile of orphan and ultra-orphan diseases has prompted the development  
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20 of new therapies with narrow indications. High continuing costs are likely to be a feature of  
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22 the novel lipid-lowering, hypertensive or obesity therapies being developed and especially  
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24 those developed for orphan indications. It is likely that the microsomal transfer protein  
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26 inhibitor lomitapide [45]; or the apolipoprotein B anti-sense oligonucleotide mipomersen[46]  
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28 for severe hypercholesterolaemia will have high prices suited to their orphan indications for  
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30 homozygous familial hypercholesterolemia in addition or as an alternative to apheresis rather  
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32 than more general usage.  
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38 Type I and type V hyperlipidaemia are encountered in lipid clinics and are associated  
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40 with pancreatitis and secondary diabetes. The primary therapies of fibrates, niacin, statins and  
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42 omega-3 fatty acids are unsuccessful in patients with homozygous null mutations (often type I  
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44 disease) of lipoprotein lipase (LPL) or its cell surface receptor GPIHBP1. They may be more  
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46 useful in rescuing LPL deficiency secondary to deficiency of its activating co-factor  
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48 apolipoprotein C2. However these drugs are most effective in type V hyperlipidaemia caused  
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50 by the combination of heterozygous LPL deficiency allied with insulin resistance [47, 48].  
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55 Apart from supportive measures, bed rest and high dose anti-oxidants allied with acute  
56  
57 plasmapheresis little can be done for type I hyperlipidaemia and therapeutic control can  
58  
59 remain elusive. A few reports have suggested benefits of reducing chylomicron production by  
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3 inhibiting fat absorption through prescription of the gastric lipase inhibitor orlistat[49]. Some  
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5 case reports exist of occasional patients treated by bilio-pancreatic bypass surgery with  
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7 claimed success [50, 51] in addition to the usual surgical management of the complications of  
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9 recurrent pancreatitis. The potential alternative therapy for homozygous LPL deficiency is  
10  
11 alipogene tiparvovec gene therapy for hypertriglyceridaemia which may be curative for LPL  
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13 gene mutations and does reduce the incidence of pancreatitis but is likely to be extremely  
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## Conclusion

It would be ironic if the next treatments for refractory hyperlipidaemia, hypertension or diabetes became surgical for reasons of superior cost economics as surgical procedures involve only a single intervention and lower follow-up costs as compared to high and continuing costs for pharmacological interventions (at least until expiry of any relevant patent)[53].

## Declaration of Interest

ASW has received lecture honoraria from Aegerion Pharmaceuticals.

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